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ABSTRACTS

Section
Analytical Methods Drugs and Medicines
PHARMACOKINETICS OF EFAVIRENZ: COMPARATIVE STUDY OF ACTIVE PHARMACEUTICAL INGREDIENT AND POLYMERIC SOLID DISPERSION IN RABBITS

JONATA AUGUSTO OLIVEIRA¹, EVELIN DOS SANTOS MARTINS¹, TAÍSA BUSARANHO FRANCHIN¹, CAROLINE DAMICO CANDIDO¹, PEDRO JOSÉ ROLIM-NETO², ROSÂNGELA GONÇALVES PECCININI¹

¹FCF - UNESP - School of Pharmaceutical Sciences São Paulo State University, Araraquara, SP; ²UFPE - Federal University of Pernambuco, Recife, PE

Introduction: Efavirenz (EFZ) is the first-line drug used to treat acquired immunodeficiency - AIDS due to its high viral suppression potency, however it is classified as Class II (low solubility and high permeability). The low solubility has significant impact on enteral absorption, resulting in high variability of bioavailability. The Laboratory of Medication Technology (LTM) produced a new solid dispersion (DS) with the objective of increasing EFZ solubility in order to improve its oral absorption. Methods: The aim of this study was to evaluate and compare pre-clinical EFZ pharmacokinetics in albino rabbits (males, 2.8 kg; n = 21) (CEUA/FCF/Car: 13/2016) after oral administration of the active pharmaceutical ingredient (50 mg) (ORAL-IFA) and carried by DS (50 mg - 10% EFZ) (ORAL-DS). EFZ quantification was performed using a validated UHPLC method and the pharmacokinetic parameters were obtained using calculations for one-compartmental model. Results and discussion: No significant statistical differences were observed in EFZ pharmacokinetic parameters, however lower intra-group variability was observed in the absorption parameters for the ORAL-DS group. The variability of results for ORAL-IFA and ORAL-DS was: Cl 73.33% and 27.55%; Vdarea 83.93% and 70.18%; t1/2 94.85% and 57.99; Cmax 62.69% and 48.20% and F 59.79% and 41.67%, respectively. Conclusion: The DS contributes positively to decrease the high variability of EFZ plasma concentrations, grounding future studies in other animal models and later clinical studies, with a view to its implementation in therapeutics. Support: CNPq (134347/2016-1); FAPESP (2015/23843-9).

IN VIVO PERSPECTIVES FROM IN VITRO ASSAYS

TAÍSA BUSARANHO FRANCHIN¹, BRUNA CRISTINA ULIAN SILVA¹, RONE APARECIDO DE GRANDIS¹, JOÃO PAULO DOS SANTOS FERNANDES², MICHEL LEANDRO DE CAMPOS³, ROSÂNGELA GONÇALVES PECCININI¹

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Introduction: Tuberculosis is still present in the majors’ causes of death worldwide and with the increase of drug resistance cases, the development of new drugs become crucial. The Federal University of São Paulo (UNIFESP) developed prodrugs of pyrazinoic acid (POA), and the in vitro screening of the new compounds, analyzing LogP, stability in different buffers and Apparent Permeability (Papp) of the molecules POAEt, POAEtPOA, POAMe, and POABu will help in the prevision of their pharmacokinetics. Methods: LogP was determined with shake-flask method, in three proportions of Water/Octanol (1:1; 2:1; 1:2), the chemical stability of compounds was performed in different buffers (pH 1.2; 7.4; 8.8) and to define the Papp, the compounds were submitted to the Caco-2 monolayer system in Hanks buffer, with fluorescein and verapamil as low and high permeability controls. All these analyses were quantified by developed methods in UHPLC. Results and discussion: The LogP values vary from -1.60 to -1.20, indicating the hydrophilicity of the molecules, which may difficult their absorption by the cell membranes. In general, the compounds presented a high stability in the 7.4 and 8.8 pHs, and stable up to 24h, however, in the pH 1.2 they show an accentuated instability, indicating the need of protection against acid pHs since it is expected their oral administration. Papp was considerate moderate, with values from 1.66 to 4.66x10⁻⁶ cm/s. Conclusions: Although their hydrophilicity, the compounds showed a prevision of moderate absorption, being necessary only the protection against acids pHs, indicating a good perspective in the continuity of development. Financial Support: FAPESP (2016/23229-1; 2016/04927-0; 2011/11239-9)
DYE ADSORPTION TO POLYMERIC NANOPARTICLES BY ASYMMETRIC FLOW FIELD FLOW FRACTIONATION

THAÍS GODINHO PONTÍFICE¹, GWENALLE ELZA NATHALIE POUND-LANA², VANESSA CARLA FURTADO MOSQUEIRA¹,²

¹Post-graduation program in pharmaceutical sciences (CiPharma), Federal University of Ouro Preto, MG, Brazil, ²Post-graduation program in pharmaceutical nanotechnology (PPGNanoFarma), Federal University of Ouro Preto, MG, Brazil

Introduction: Surface lipophilicity of drug nanocarriers influences the drug delivery profile and interaction with biological media, thus playing a decisive role in their in vitro and in vivo performance. However, the techniques described in the literature to characterize materials surface properties are difficult to apply to nanostructured systems. The gold standard in nanocarrier pre-clinical tests is the method of Rose Bengal adsorption, but it requires NP separation from the aqueous continuous phase. This study reports the use of asymmetric flow field flow fractionation (AF4) with UV, fluorescence, static and dynamic light scattering detection (AF4-MALS-DLS-UV-FLD) to characterize the surface lipophilicity of biodegradable polyester-based nanoparticles used as drug delivery systems.

Methods: Aqueous suspensions of blank polyester nanoparticles were incubated with Rose Bengal and analyzed by AF4-MALS-DLS-UV-FLD to separate the nanoparticles and determine their size and amount of adsorbed dye.

Results and discussion: The levels of fluorescence detected by AF4, which strictly corresponds to the dye associated to the NP fraction of the samples, varied as a function of the NP content in the sample. Thus, a graph relating the fluorescence intensity to the NP surface area could be constructed, enabling a comparison between surface lipophilicity of the selected polyester nanoparticles. Conclusions: AF4-MALS-DLS-UV-FLD complements the existing method of Rose Bengal adsorption to determine the lipophilicity of biomaterials in nanostructured form. As the technique offers simultaneous determination of the nanoparticle size and size-distribution, this additional lipophilicity evaluation makes it a powerful technique in nanocarrier physico-chemical characterization.

Acknowledgements: The authors thank INCT-NANOFARMA (CAPES #2014/50928-2 and CNPq #465687/2014-8), FAPEMIG (APQ-02864-16), CNPq (310463/2015-7) and UFOP, Brazil, for financial support.

CHEMICAL STABILITY OF BIODEGRADABLE POLYMERIC NANOCARRIERS STUDIED BY GEL PERMEATION CHROMATOGRAPHY AND FIELD FLOW FRACTIONATION

SABRINA EMANUELLE DIAS SILVA¹, MARIA ALICE DE OLIVEIRA¹, GWENALLE POUND-LANA², VANESSA CARLA FURTADO MOSQUEIRA¹,²

¹Post-graduation Program in Pharmaceutical Sciences (CiPharma), Federal University of Ouro Preto, MG, Brazil, ²Post-graduation Program in Pharmaceutical Nanotechnology (PPGNanoFarma), Federal University of Ouro Preto, MG, Brazil

Introduction: Poly(alpha-hydroxy esters), such as poly-D,L-lactide (PLA) and its copolymers with polyethylene glycol (PLA-PEG) are widely used in drug delivery devices due to their biodegradable and bioreversible character. This study evaluates the use of gel permeation chromatography (GPC) and asymmetric flow field flow fractionation with dynamic and light scattering detectors (AF4-DLS-MALS) to determine the kinetics of and provide mechanistic insights into the degradation of the polymers in nanostructured form. Methods: Polymeric nanosphere aqueous suspensions were obtained by nanoprecipitation and maintained at 37°C in water (pH 7 or 1) or in aqueous medium containing with fetal bovine serum. Samples were withdrawn over time, analyzed for nanoparticle size and morphology by AF4-DLS-MALS or analyzed by GPC for polymer molar mass determination.

Results and discussion: The nanospheres maintained their colloidal stability with sizes in the 60-90 nm range in water and in medium containing serum for up to one week. AF4 analysis indicated a slight increase in the size distribution of the sample in serum, presenting larger nanoparticles than the initial sample, which will be discussed in the light of GPC analyses currently under way. Conclusions: AF4-DLS-MALS combined to GPC provide complementary data to study the kinetics and mechanisms of polymer degradation, which are valuable in pre-clinical evaluation of polymeric drug nanocarriers.

Acknowledgements: The authors thank INCT-NANOFARMA (CAPES #2014/50928-2 and CNPq #465687/2014-8), FAPEMIG (APQ-02864-16), CNPq (310463/2015-7) and UFOP, Brazil, for financial support.
STABILITY-INDICATING HPLC METHOD AND CHEMICAL CHARACTERIZATION OF FORCED DEGRADATION PRODUCTS OF CATECHOLAMINES

LETÍCIA COLI LOUVISSE DE ABREU¹, GIL VIANA¹, ALICE SIMON¹, EDUARDO PINTO¹, LUCIO CABRAL¹

¹UFRJ - Universidade Federal do Rio de Janeiro, RJ, ²IFRJ - Instituto Federal do Rio de Janeiro, Duque de Caxias, RJ

Introduction: Catecholamines (CA) are an important class of neurotransmitters in mammalian central and peripheral nervous systems. Epinephrine and norepinephrine are used in therapy combined with local anesthetic agents because of their vasoconstriction action, thus extending the duration of local anesthesia and reducing bleeding. A major problem of pharmaceutical formulations containing epinephrine or norepinephrine is the low stability of these drugs in solution. In this way, the purpose of this study was to identify and characterized CA degradation products.

Methods: Catecholamines degradation was tested under forced conditions including alkaline and acidic hydrolysis, oxidation, metallic and photolysis according ICH guideline. The suitability of epinephrine and norepinephrine stability-indicating method was evaluated by the use of a RP-18 column in isocratic elution using octane sulphonate ion pair and methanol as mobile fase. DPs resulted from hydrolysis, oxidative and metallic degradation were subjected to the liquid-liquid extraction with ethyl acetate. All those fractions were analyzed by TLC and HPLC-DAD. Isolated DPs by preparative TLC were characterized by high resolution mass spectrometry (HRMS), 1H-NMR, 13C-NMR and infrared (IR) spectroscopy.

Results and discussion: Forced degradation of CA led to the formation of three DPs which have never been previously reported as CA degradation products.

Conclusions: The identification and characterization of CA DPs enabled us to understand not only the drug’s behavior in stressful conditions, but also its DPs formed.

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HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD DEVELOPMENT AND VALIDATION FOR THE QUANTIFICATION OF A HYDROPHOBIC NIR DYE IN POLYMERIC NANOCARRIERS

MARINA GUIMARÃES CARVALHO¹, MARIA ALICE DE OLIVEIRA¹, GWENNAELLE POUND-LANA², VANESSA CARLA FURTADO MOSQUEIRA¹,²

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Introduction: Encapsulation of cancer chemotherapeutics in biodegradable polymeric nanocarriers is a strategy used to reduce the drug side-effects and improve its efficacy. Near infrared (NIR) fluorescent dyes, such as IR-780, are promising both as molecular imaging label and photosensitizer, with potential in cancer theranostics. This work presents the development and validation of an analytical method for IR-780 quantification in polymeric nanocarriers developed in our group.

Methods: A high-performance liquid chromatography method was developed and validated according to resolution RDC 166 of the National Health Surveillance Agency (ANVISA) and ICH guidance for validation of analytical procedures. Chromatographic analysis was achieved on a C18 column, using an isocratic mobile phase consisting of acetonitrile:water (65:35) with 0.1% acetic acid, at 30 °C, flow rate of 1.0 mL/min and UV detection at 700 nm. The method was selective and linear in the range of 0.1 – 10.0 µg/mL (r²= 0.9998), precise and exact with values between 0.26 – 3.29 % and 99.32 – 100.77%, respectively. Limits of detection and quantification were 0.01 and 0.04 µg/mL, respectively.

Conclusions: A high-performance liquid chromatography (HPLC-UV) method precise and exact was developed and validated. The method was suitable for the quantification of IR-780 in the nanocarriers and will be of great importance for the ongoing development and their pre-clinical evaluation of antineoplastic drug nanocarriers.

Acknowledgements: The authors thank INCT-NANOFARMA (CAPES #2014/50928-2 and CNPq #465687/2014-8), FAPEMIG (APQ-02864-16), CNPq (310463/2015-7), CAPES and UFO, Brazil, for financial support.
A STABILITY-INDICATING HPLC METHOD FOR A THIAZOLYL HYDRAZONE DERIVATIVE WITH ANTIFUNGAL ACTIVITY

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Background: The 2-[2-(cyclohexylmethylene)hydrazinyl]-4-phenylthiazole (RN104) was previously evaluated in vitro and in vivo and showed interesting results against Cryptococcus gattii and Cryptococcus neoformans. Cryptococcosis is an opportunistic or primary fungal infection that can infect humans, leading to severe clinical conditions. The limited number of available drugs for the treatment of this disease, together with concerns to the toxicity and development of resistance, has encouraged the search for new drugs. Objectives: To perform forced degradation studies to investigate the chemical behavior of the molecule and to develop and validate an analytical method for its quantification. Methods: RN104 was submitted to degradation under neutral, acid and alkaline hydrolysis, temperature, oxidation, metals ions and light conditions. The results were used on the development of a stability indicating method by HPLC. Kinetic study was also carried out. Results and discussions: The analytical method showed selectivity, precision, accuracy, robustness and linearity in the range of 0.02 - 0.24 mg/mL of RN104 in accordance with current legislation. The assay involved an isocratic elution in a C18 column using a mobile phase composition of water and acetonitrile (15:85 v/v) and the column temperature was set at 30º C. The flow rate was 1.2 ml/min and the analyte monitored at 240 nm. The results obtained in degradation studies demonstrated that RN104 is sensitive to alkaline conditions and the presence of metal ions. Conclusions: The stability-indicating method proved to be selective for RN104 and its degradation products (DP). The DP will be isolated, identified and their formation mechanisms will be investigated. Financial support: FAPEMIG, CNPq

VALIDATION OF AN HPLC-UV METHOD TO ASSAY N,N-diethyl-m-toluamide (DEET) IN DIFFERENT REPELENT FORMULATIONS

JULIANA DOS SANTOS¹, REBECA LINO LOURENÇO¹, ALIENI BITENCOURT DE SOUZA¹, ANDRÉA INÊS HORN ADAMS¹

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Introduction: N,N-diethyl-m-toluamide (DEET) is the most common repellent substance used on insect control. In Brazil, it is sold as aerosol, solution, lotion and gel, in concentrations ranging from 6.65 to 25%. Infrared spectroscopy is the pharmacopeial method, using carbon disulfide as solvent. A survey on literature revealed the development of chromatographic methods to assay DEET in biological matrices. However, there are no analytical methods reported to assay DEET formulations. Considering the wide applicability of chromatography in pharmaceutical analysis, the objective of this study was to develop and validate a stability indicating HPLC method for the DEET determination in three different formulations: solution, lotion and gel. Methods: The method employed a Shimadzu chromatographic system, equipped with PDA detector, mobile phase composed by methanol, acetonitrile and water pH 4.5 (45:10:45), flow of 1.0 mL/min, detection at 270 nm and RP-18 column. The linearity was studied in the concentration range of 2.5–100 µg/mL. The accuracy was carried out by the spiking method and the precision was evaluated in two levels: repeatability and intermediate precision. Sample solutions were exposed to stress conditions to study the method specificity and purity peak in all the stress conditions was accessed. The robustness was evaluated by a factorial design 2² and the chosen factors were pH, the proportion of water and the flow rate of mobile phase. Results and discussion: The method was linear in the range of 2.5–100 µg/mL, with linear regression and absence of deviation from linearity. The mean recoveries were 99.56%, 100.18% and 99.49% for the lotion, solution and gel, respectively (n=9 for each formulation), which are in agreement with the recommended values. Method also demonstrated suitable precision for all formulations, since in both studied levels the RSD values were < 2%. In all stress test conditions the DEET peak was pure, demonstrating the method specificity. No interference from the excipients was observed. The robustness assessment showed no significant effect of individual factors or of their interaction (p > 0.05). Conclusion: A simple and stability-indicative method was developed to determine DEET in repellents. The method was applicable to assay the drug in solution, lotion and gel, with the same experimental conditions. Financial Support: CAPES, FIPE SÊNIOR-UFSM and FIT-UFSM.
DEVELOPMENT AND VALIDATION OF A SPECTROPHOTOMETRIC UV DISSOLUTION METHOD FOR EMPAGLIFLOZIN TABLETS

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Introduction: Empagliflozin is a drug used in the treatment of Diabetes mellitus type 2, which inhibits the glucose reabsorption in the kidneys. The drug was approved by FDA in 2014 and until now, no methods to determine empagliflozin tablets have been reported in pharmacopeias. The objective of this work was to develop the first dissolution method for empagliflozin coated tablets, by a simple UV-method. Methods: The sink condition in several media (pH range of 1.2 to 6.86) was determined and phosphate buffer pH 6.86 was chosen as dissolution medium, at 37ºC ± 0.5. After initials tests, rotation speed was determined as 40 rpm. Subsequently, the method was validated according USP guidelines, by the parameters of specificity, linearity, precision, accuracy and filter suitability evaluation. Results and discussion: In the specificity evaluation, the placebo interference was calculated and the value of 1.63% was obtained, which met the requirements. Conclusions: A simple UV-method to evaluate the dissolution of empagliflozin tablets was developed and validated. This method can be used in the batch-to-batch evaluation, contributing to the quality control of this pharmaceutical product. Financial Support: CNPq, FIPE Sênior-UFSM.

POTENTIAL ANTI-INFLAMMATORY ACTIVITY OF A NEW N-ACYLHYDRAZON DERIVATIVE

MARIA CRISLANDIA FREIRE DE ALMEIDA ALMEIDA¹, NADJAELE MELO APOLINÁRIO¹, MARIA ELAINE CRISTINA ARARUNA², RAIFF S. DANTAS², ITALIA SAMARA DA SILVADIAS¹, WILLIAN CHARLES DA SILVA Moura¹², RENALY IVYNA DE ARAÚJO RÊGO¹, PABLO RAYFF SILVA¹, RICARDO OLIMPIO DE MOURA¹², VANDA LUCIA DOS SANTOS¹²

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Acylhydrazone derivatives stand out as an important class of synthetic chemical compounds for their diverse biological properties as analgesic and anti-inflammatory. This study aimed to characterize and evaluate the anti-inflammatory potential of the N-acylhydrazonic derivative (JR09). The compound was characterized for efficiency, melt temperature and LogP. Adult Swiss albino mice were used in the models of peritonitis and paw edema induced by carrageenan and pockets of subcutaneous air. The acute toxicity test was also performed. The experimental protocols were approved by the Committee of Ethics in the Use of Animals of the Center of Higher Education and Development (n°: 5905022016). The compound showed an efficiency of 89%, showing good viability of the synthetic route adopted, melting temperature variation of 3ºC, ensuring compound purity and LogP of 1.21 indicating a good bioavailability and chemical shift signals in 1H NMR spectra and 13 C-DEPT-Q NMR characteristic of the structure as N'-(benzylidene)-2-cyanoacetohydrazide (JR09). The compound at dose 10 mg.kg⁻¹ inhibited cell migration in 59% and 66% for carrageenan-induced peritonitis and subcutaneous air pocket models, respectively. In paw edema, the compound significantly reduced edema at 35, 86 and 75% in the second, third and fourth hours, respectively, and the serum concentration of C-reactive protein when compared to the control group. Assessment of acute toxicity at the dose of 100 mg / kg indicated low toxicity. The results obtained indicate the N-acylhydrazone derivative JR19 with potential for future use as anti-inflammatory. Financial Support: CNPq and UEPB.
CAPILLARY ZONE ELECTROPHORESIS METHOD FOR THE QUANTITATION OF MONOCLONAL ANTIBODY DENOSUMAB

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Introduction: Denosumab (DmAb), a fully human monoclonal antibody produced by recombinant engineering techniques, is a category of targeted therapeutic agents approved for the prevention and treatment of postmenopausal women with osteoporosis at high risk of fracture, and giant-cell tumor of bone. The structure consists of 2 heavy chains and 2 light chains, with 447 and 215 amino acids each, respectively, with a molecular mass of 147 kDa. The aim of this study was to develop a capillary zone electrophoresis (CZE) method for the analysis of DmAb in biopharmaceutical products.

Methods: A fused-silica capillary (50 µm i.d.; effective length, 40 cm), maintained at 25 ºC, was used. The applied voltage was 20 kV. A background electrolyte solution consisted of 40 mmol/L sodium tetraborate buffer and the internal standard was nimesulide. Injections were performed using a pressure mode at 50 mbar for 5 s, and detection at 200 nm.

Results and discussion: Separation was obtained with migration time of 3.5 min. The specificity was confirmed by forced degradation studies, interference of excipients and peaks purity. The calibration curve was linear over the range of 5−300 µg/mL (r²=0.9998), and the quantitation limit was 5 µg/mL. The method was applied for the quantitative analysis of DmAb, giving values between 94.23 and 102.42% of the stated potency.

Conclusion: The results obtained showed the capability of the CZE method, as an alternative, that can be applied for the analysis of DmAb, contributing to improve the quality control and to assure its therapeutic efficacy.

Financial supports and acknowledgements: CAPES and FATEC.

IN VITRO ASSAYS OF NEW COMPOUNDS FOR TREATMENT OF LEISHMANIASIS AND TRYPANOSOMIASIS

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Introduction: Visceral leishmaniasis and trypanosomiasis are diseases that affect thousands of people every year. Besides being neglected illness, treatments are insufficient, invasive and cause serious adverse effects. The Federal University of São Paulo (UNIFESP) developed the compounds LINS03006 and LINS03013, derivatives of gibbilimbol, that present in vitro activity against Leishmania infantum and Trypanosoma cruzi. In vitro assays can be used to predict pharmacokinetic properties improving the design of pre-clinical studies: stability in different buffers, logP and apparent permeability (Papp).

Methods: The chemical stability test has performed in buffers 1.2, 7.4 and 9.0. The logP has determined using Shake Flask method with water and octanol in different proportions. The permeability assays have realized in human colorectal adenocarcinoma cells (Caco-2) and apparent permeability (Papp) was calculated. The compounds quantification was performed through UHPLC/UV methods previously developed.

Results and discussion: At the pH 1.2, the compound LINS03006 showed a high stability (24 h), whereas the LINS03013 showed low stability (5 min), it is unstable at acid pH, requiring a formulation to protect it from the stomach pH. At pHs 7.4 and 9.0 the logP was determined using Shake Flask method with water and octanol in different proportions. The permeability assays have realized in human colorectal adenocarcinoma cells (Caco-2) and apparent permeability (Papp) was calculated. The compounds quantification was performed through UHPLC/UV methods previously developed.

Conclusion: The compounds have been shown to be promising for future in vivo studies and the elucidated characteristics should be considered in the pre-clinical planning.
DEVELOPMENT AND VALIDATION OF AN RP-HPLC METHOD FOR THE DETERMINATION OF INSULIN FROM LIPOSOMES FOR POTENTIAL NASAL ADMINISTRATION

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Introduction: Insulin (INS) is a protein clinically employed for the treatment of diabetes through subcutaneous injections. However, nasal delivery of insulin remains an attractive alternative to parenteral delivery. In this study a simple RP-HPLC method was developed and validated for the quantification of INS in liposomes (LIP) intended for nasal delivery. Methods: The method was validated using Waters HPLC and C18 column maintained at 25°C. A mixture of acetonitrile and 0.1% TFA aqueous solution (60:40, v/v) was used as mobile phase with flow rate of 1.0 mL/min, the injection volume was 20 µL and detection was 214 nm. Calibration curve (1 to 100 µg/mL) were prepared in PBS pH7.4 and analyzed three times. The validation parameters evaluated were linearity, selectivity, precision, accuracy, detection and quantitation limits and robustness, according RDC 166/17. Results and discussion: The calibration curve was linear (1 to 100 µg/mL) with a correlation coefficient of 0.9995. The specificity was demonstrated through the injection of PBS pH7.4, mobile phase and blank LIP, showing no interferences with the peak of interest. The values obtained for the intra-day and inter-day precision tests were 1.54% and 1.25%, respectively. The accuracy was proven by the recovery test, with an average of 99.5%. Detection and quantitation limits were found to be 0.27 and 0.82 µg/mL, respectively. The robustness was assessed varying flow rate, mobile phase composition and temperature and the recovery was considered adequate (80-120%). Conclusion: The results demonstrated that the analytical method was adequate and will be used to predict the encapsulation efficiency and release profile of insulin from LIP.

Financial Support and Acknowledgements: CAPES; CNPQ; FUNDUNESP; PADC; Fapesp;

DEVELOPMENT OF EMPAGLIFLOZIN SUSPENSIONS AND STABILITY ASSESSMENT

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Introduction: Empagliflozin (EMP) is an inhibitor of sodium–glucose cotransporter 2 used to treat patients with type 2 diabetes, which is sold as tablets (10 and 25 mg, Jardiance®). In clinical hospital practice, sometimes is necessary to adapt the available pharmaceutical forms, in order to meet specific patient demands. The goal of this work was to develop and evaluate the stability of empagliflozin in extemporaneous formulations aiming to obtain stable formulations suitable for hospital use. Methods: Suspensions containing 2 mg/mL EMP were prepared from the powder of the crushed and sieved tablets. Two different polymers were used in suspensions: hydroxymethylcellulose (F1) and carboxymethylcellulose (F2). Methylparaben and propylparaben were used as preservatives, pH was adjusted to 6.5 and the volume was made up with ultrapure water. The sedimentation volume, particle size, pH, viscosity EMP assay and microbial limits were evaluated just after preparation (zero time) and over 25 days of storage (25°C). The suspensions were assayed by a MEKC method, previously validated by our group. The microbial limit was estimated by the number of viable aerobic microorganisms. Results and discussion: At zero time (t0) the results for F1 and F2 were, respectively: pH 6.5 ± 0.03 and 6.51 ± 0.02; particle size, 77.23 ± 1.47 and 102.33 ± 0.88; sedimentation volumes, 0.06 ± 0.003 and 0.310 ± 0.012; assay, 100.69 ± 0.017 and 101.71 ± 0.07. After 25 days of storage, the pH and sedimentation volumes did not differed statistically (p>0.05) from the initial value for both formulations. The particle size of F1 (81.67 ± 2.54) and the assay (97.64 ± 0.23) were different from the values obtained on zero time (pConclusions: Two oral suspensions with satisfactory physicochemical characteristics were developed: pH compatible with oral use, adequate drug content and microbiological count within the limits. The preliminary data suggest the lower stability of F1, considering the decrease in EMP content and the low sedimentation volume, also evidenced by compact sediment, interfering on redispersion and correct dosage. Financial Support: CAPES, Fipe Sênior/UFSM, FIT/UFSM
QUALITY CONTROL AND VALIDATION OF AN ANALYTICAL METHODOLOGY FOR THE QUANTIFICATION OF CHLOROGENIC ACID IN COATED TABLETS OF ARTICHOKE (Cynara scolymus L.) BY HPLC

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Introduction: The artichoke (Cynara scolymus L.) is a plant from the family Compositae that originates in the Mediterranean, but due to its alimentary properties, is already found all over the world. Artichoke leaves also have pharmacological properties that are associated with their secondary metabolites, especially phenolic compounds. Its extracts may be incorporated into syrups, solutions and excipients to give the tablets and capsules. At the end of 2008, ANVISA published NI 5 which contains the list of herbal medicines with simplified registration, in which the artichoke is recommended as choleretic and cholagogue. Objectives: To contribute to the phytochemical study of species and to demonstrate that the developed method for the chlorogenic acid determination is safe and reliable. Methods: Coated tablets produced with dry artichoke extract in the quality control laboratory of the Federal University of Paraíba were submitted to quality control analysis and analytical validation by HPLC. Results: The product met the specifications of the official monographs and has quality to be produced for commercialization. It was concluded that the analytical methodology developed by HPLC for the determination of chlorogenic acid in artichoke-coated tablets (Cynara scolymus L.) has high specificity, precision (RSD < 5%), linearity (r > 0.99), accuracy (RSD < 5%) and was robust against the submitted variations, being thus considered validated and suitable for the assay of the label. Conclusions: According to the results obtained, it can be concluded that the proposed analytical method is validated and, therefore, suitable for use in the routine of quality control laboratories.

ID: 158

A POLYMERIC NEAR-INFRARED CARBOCYANINE DYE FOR BIODEGRADABLE NANOCARRIER FLUORESCENCE LABELING

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Introduction: Fluorescent near-infrared (NIR) dyes are useful to monitor nanocarriers in vivo and can serve as photosensitizers in cancer therapy. However, new strategies need to be developed in order to guarantee that the dye photo-physical properties and dye loading within the nanocarrier remain stable. This work reports the facile chemical conjugation of a carbocyanine NIR dye to polylactide (PLA) for stable fluorescent labeling of biodegradable polymeric nanocarriers. Methods: PLA was synthesized via organocatalyzed ring-opening polymerization of D,L-lactide with an activated alkyne functional initiator. The dye was derivatized and conjugated to PLA via a one-pot catalyst-free azide-alkyne cycloaddition (AAC) reaction. The success of the reaction was evaluated by high performance liquid chromatography (HPLC) and gel permeation chromatograph (GPC). Nanospheres containing the dye – polymer conjugate were prepared by nanoprecipitation and characterized by asymmetric flow field-flow fractionation with light scattering and fluorescence detection (AF4-MALS-FLD). Results and discussion: Conjugation of the NIR dye to PLA was confirmed by HPLC and GPC. Nanospheres showed reduced size (Conclusions: The synthetic methodology used was effective to promote conjugation of a NIR fluorescent dye to PLA. The fluorescent nanospheres showed characteristics suitable for their use in pre-clinical imaging in vitro and in vivo in biodistribution studies. Acknowledgements: the authors thank INCT-NANOFARMA (CAPES #2014/50928-2 CNPq #465687/2014-8), FAPEMIG (APQ-02864-16), CNPq (310463/2015-7), CAPES and UFOP, Brazil, for financial support.
DEVELOPMENT OF A SIMPLE ANALYTICAL METHOD FOR SIMULTANEOUS DETERMINATION OF CLINDAMYCIN PHOSPHATE AND RIFAMPICIN IN SKIN PERMEATION TESTS

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Introduction: Severe diseases that affect the hair follicles are commonly treated with the combination of antibiotics, such as clindamycin phosphate and rifampicin. However, there is still a need for an analytical method capable of identifying these drugs against the biological skin matrix. Objective: This work proposes the development of a simple and sensitive analytical methodology capable of detecting/quantifying clindamycin phosphate and rifampicin in the skin layers using high performance liquid chromatography. Method: Parameters of linearity, selectivity, limits of detection and quantification and precision were evaluated. In addition, the best extractive conditions of the two drugs from the different skin layers were optimized. Determinations were performed using UV-Vis detector at the wavelength of 200 nm and 238 nm for clindamycin phosphate and rifampicin, respectively. The efficient chromatographic separation of clindamycin phosphate and rifampicin was succeeded using a C18 column (150 mm x 4.6 mm, 5 μm), with gradient elution of the mobile phase composed of 0.01 mol L-1 phosphoric acid and methanol at a flow rate of 1 mL min-1. Results and discussion: The retention times for clindamycin phosphate and rifampicin were approximately 7.4 and 12.2 min, respectively. The method was precise (values of coefficient of variation < 4.03% for clindamycin phosphate and < 4.04% for rifampicin) and linear (r² = 0.99913 for clindamycin phosphate and r² = 0.99951 for rifampicin) with regression curve in the concentration range from 0.5 to 20.0 μg mL-1 and recovery rates from the skin layers higher than 85%. The presence of skin components did not interfere with the analysis. Conclusion: The validated method was therefore appropriate for quantification of both clindamycin phosphate and rifampicin and thus may be feasible to be used in skin permeation studies.

Acknowledgements: The authors acknowledge CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) and CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) for the financial support and “Bonasa Alimentos” for gently providing porcine ear.

ID: 185

EVALUATION OF TRANSDERMAL DELIVERY OF METFORMIN HYDROCHLORIDE FROM A SEMISSOLID VEHICLE

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Introduction: Metformin hydrochloride is a traditional, FDA-approved active pharmaceutical ingredient (API) used as first line drug of choice to treat type 2 diabetes. It has being researched to be effective in other injuries, including ageing-related processes. This ex vivo study aimed to evaluate the use of a commercial transdermal vehicle as a semisolid, liposomal vanishing cream to deliver metformin hydrochloride through the human skin. Methods: The experiments consisted in a percutaneous absorption assay in Franz diffusion cells coupled with freshly excised human skin and analysed by high performance liquid chromatograph (HPLC). Quantification was performed using a validated method. This study was conducted in compliance with the Brazilian guidelines and Ethics, had its approval obtained from the local committee of Federal University of Juiz de Fora (approbation no. 151.275). Results and discussion: Percentage of permeation of transdermal metformin hydrochloride was 46.7% from the applied dose (equal to 11 mg), which is close to the percentage of the oral administration absorption (about 50% of the drug). This corresponds to 93.4% of the oral dosage, and probably without the side effects that are commonly presented by patients. Conclusion: The results showed that transdermal metformin hydrochloride could be an option for patients searching for its diverse clinical effects without suffering gastro-intestinal side effects and avoiding first-pass metabolism.
EX VIVO SKIN PERMEATION EVALUATION OF A TRANSDERMAL OXANDROLONE EMULSION

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Introduction: Oxandrolone is a potent synthetic testosterone analogue that possesses strong anabolic property and weak androgenic activity. Oral oxandrolone can potentially promote several adverse effects. The transdermal delivery of drugs may represent a means to avoid or minimize oral adverse effects. Thus, the objective of this study was to evaluate the permeability of oxandrolone in human skin on a preliminary basis for possible future determination of the transdermal route as an alternative treatment.

Methods: We used a percutaneous absorption assay in Franz diffusion cells coupled with freshly excised human skin (approved by Ethics Committee of University Federal of Juiz de Fora, protocol no. 151.275). The drug release kinetics were determined to predict the efficiency of the transdermal route. Results and discussion: Nearly 236 μg (86.7%, in terms of applied dose) of the product was prevented to permeate due to the barrier function of the stratum corneum (SC); 21.6% reached the receptor medium (RM), and the remaining 4.3% were quantified within viable layers of the skin (in vivo, dermis is vascularized). The total amount of drug able to exert effect is the sum of the drug quantified within remained skin (RS) and RM: then, a total of 247.6 μg of oxandrolone (25.9% of the applied dose) would be able to permeate through a non damaged skin. The accuracy of the data is demonstrated by the calculated mass balance (average recovery = 112.6%). Conclusion: Transdermal oxandrolone could be a viable alternative for traditional oral form, once clinical studies are conducted to prove this hypothesis.

TAXIFOLIN: A POLYMORPHISM STUDY

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Introduction: Taxifolin (Tax) is a flavonoid which presents hepato, cardio, gastro and neuroprotective effect and has been isolated from the seeds of Mimusops balata with high purity. To consider Tax as a potential new drug, it is necessary to determine the presence of polymorphs. Methods: Tax was dissolved in 9 different solvents: acetone (1), acetonitrile (2), anhydrous acetonitrile (3), chloroform:methanol 90:10 (4), dichloromethane:ethanol 95:5 (5), ethanol 95% (6), absolute ethanol (7), ethyl acetate (8) and methanol (9), and evaporated at room temperature. The crystals were analyzed by X-ray, differential scanning calorimetry (DSC), thermogravimetry (TGA), infrared spectroscopy (FT-IR) and scanning electron microscopy (SEM). Results and discussion: X-ray diffraction patterns showed that the starting Tax displays four cells (phases 1 to 4). Phase 1 was observed for samples obtained from solvents 1, 4, 5, 6 and 9, phase 2 for solvent 8, phase 3 for solvent 2, and phase 5 and phase 6 for solvents 3 and 7, respectively. After crystallization with solvents 2, 3, 7, 6, 8 each polymorph presented different melting point/water weight loss: 236.98°C/11% (starting Tax powder); 237.06°C/5.65% (2), 234.01°C/3.91% (3); 238.42°C/0% (7); 236.85°C/10.95% (6); 237.98°C/0% (8). Crystals of samples 1, 2, 4, 6, 9 showed different sizes, similar needle shape and different organization, while the other crystals (3, 5, 7, 8) exhibited different shape and size between them. Conclusion: Tax polymorphism is affected by the presence of water, solvents, and temperature. Therefore, particular attention must be paid during Tax powder production. Financial support: CNPQ/CAPES edital PVE Nº 09/2014 – Process n. 88881.064960/2014-01; acknowledgements: CNPQ/CAPES and University of Perugia (UniPG), Italy.
Physicochemical and Phytochemical Characterization of Bark Powder of *Schinopsis brasiliensis*

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*Schinopsis brasiliensis* Engler is commonly used in the form of tea for the treatment of inflammation and several other pathologies. In addition to determining the pharmacological and toxicological activities of plants, other aspects of quality should be evaluated. Analytical techniques are used to characterize plant drugs, their derivatives and products. The objective of this work was to characterize the bark powder of *Schinopsis brasiliensis*. The samples of bark were collected, dried, powdered, sieved in different particle sizes (710, 355, 180, 150, 75 and 38 μm). The analyzes performed were scanning electron microscopy (SEM), density, total ash content (TAC), ashes resistant to acid (ARA), loss of drying (LOD), physicochemical analysis and pH determination. The mean values obtained by SEM were 340.9; 308.8; 351.5; 354.4; 289.2; 251.85 μm. These results demonstrate that the sieving process allowed the passage of particles larger than the apparent mash size. The density ranged from 0.278 to 0.333 g/mL. The TAC and ARA were from 8.33 to 9.45% and 0.41 and 0.86%, respectively. These values are within the standard established by the farmacopeia 2010, which indicates low contamination by inorganic non-volatile matter. The LOD ranged from 9.10 to 9.95%, therefore the drying was effective. The best particle was the one with lower size to extract the secondary metabolites by given 117 mg/g of polyphenols, 1,837 4mg/g of flavonoids and 10mg/g of tannins. These acid metabolites were confirmed with pH values between 4.94 and 5.28. The analytical techniques used were capable of tracing characteristic profiles of the plant drug, evidencing the differences in each particle size.

Thermal Compatibility by Differential Thermal Analysis (DTA) between Dexamethasone and Excipients Used in Tablets

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Synthetic glucocorticoids including the dexamethasone act to suppress the immune system, inhibiting manifestations of inflammation. Although widely used, some drugs available to the population were produced without preformulation studies during their development that ensure chemical/physical compatibility between Active Pharmaceutical Intakes (APIs) and pharmaceutical excipients. In this context, this work aimed to conduct a compatibility study between dexamethasone and excipients used in solid dosage forms. Binary physical mixtures between dexamethasone (DEX) and excipient (1:1) were prepared and analyzed by Differential Thermal Analysis (DTA). The samples were heated to 450 °C (10 °C min\(^{-1}\)). The excipients evaluated were: corn starch, pregelatinized starch, sodium starch glycollate, microcrystalline cellulose 101 and 102, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, lactose, mannitol, polyvinylpyrrolidone K-30 and talc. The DTA curve of DEX showed a typical modification of enthalpy \(\Delta H\) fusion of the drug, also the appearance and/or suppression of thermal events which suggest possible interaction of the API with all excipients tested, except talc. The results indicate that most of the excipients used in solid dexamethasone formulations show signs of interaction thermally, pointing a necessity to allow the development of drugs with proven efficacy and safety.
ANALYTICAL METHOD VALIDATION FOR QUANTIFICATION OF AMPHOTERICIN B IN MICRODIALYSATE SAMPLES

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Introduction: Amphotericin B (AmB) is an antibiotic used for treating systemic infections. In order for it to have the expected action, it must be able to access its place of action in sufficient concentrations and be in its free form. Therefore, the validation of an analytical method that can quantify AmB concentrations in the tissue is necessary to perform pharmacokinetic studies using microdialysis technique. Methods: An analytical method was developed in HPLC/UV using a C18 reverse phase column and a pre-column of the same material. The mobile phase consisted of a solution containing acetonitrile and 2% acetic acid (66:34, v/v). Isocratic elution is performed with a flow of 1.0 mL.min⁻¹ and UV detection was done at the wavelength of 408 nm. Solutions at serial concentrations of AmB (250-8000 μg/mL) and the quality controls (400, 1500 and 6000 μg/mL) were made using methanol as the reagent. Results: The method showed selectivity and linearity under the studied range since all the curves r were higher than 0.99. Intra and inter-day precision and accuracy were within the accepted range according to RDC 166/2017, the LOD and LOQ were 100 μg/mL and 250 μg/mL, respectively. Discussion and conclusions: The developed method was validated according to ANVISA and it can be used to quantify AmB in microdialysate samples in future studies.

Development institution: Pharmaceutical Sciences Post Graduate Program, Faculty of Pharmacy, Federal University of Bahia. Financial Support: FABESB and CNPq.

VALIDATION OF ANALYTICAL METHOD FOR QUANTIFICATION OF ANACARDIC ACID LOADED MICROEMULSION BY FIRST ORDER DERIVATIVE SPECTROSCOPY

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Introduction: Anacardic acid (AA) is a phenolic lipid isolated from cashew nut shell fluid reported for its pharmacological activities, its most important natural sources being plants of the Anacardiceae family. Against this, several formulations have been developed for therapeutic application. This work aims to provide the validation of AA in microemulsion systems. Methods: AA was extracted with Soxhlet with hexane, P.A., the extract was concentrated in an evaporator. For the validation of the analytical method parameters of linearity, specificity, precision, accuracy, limit of detection (LD), limit of quantification (LQ) and robustness were evaluated. Following of ANVISA RE 166/2017 and FDA's Analytical Procedures and Methods Validation for Drugs and Biologics (2015). Results and discussion: Scans were performed from 250 to 350nm of AA at 52 μg / mL, the microemulsion (ME) and the ME with 52 μg / mL AA, using ethanol PA as the solvent, where interference from absorption peaks was observed in this region, the peak of AA was at 309 nm and ME showed absorption at the same wavelength. In order to avoid error in the analysis of AA content, the spectra (250 to 350 nm) were derived in the first order (Δλ = 2) using the software UVProbe® 2.42, and absorption was verified at 326.8 nm and showed no interference of the formulation. The equation of the line obtained was y = 0.0004-0.0016, r² = 0.9941, the method is linear, selective and without interference, LD = 0.175μg, LQ = 0.265μg, precise, where the repeatability parameter presented DPR% 0.0004, and the intercurrent precision did not present a significant statistical difference for p. Conclusions: The method was linear, without interferents, precise and robust, following the current legislation. The work’s relevant because it may contribute to the characterization of new AA release systems.
L-ASPARAGINASE SUPERACTIVITY AT LOW CONCENTRATIONS OF IONIC LIQUIDS

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Introduction: The enzymatic activity of Escherichia coli L-asparaginase (ASNase), a biopharmaceutical used in the treatment of acute lymphoid leukemia, has been studied in ionic liquids (ILs), alternative green solvents, less volatile than organic solvents, with potential for enzymatic stability. The influence of alkylidine chain size on the activity of the ASNase enzyme of the ILs of the family was analyzed using 1-ethyl-3-methylimidazolium ([C2 mim]Cl), 1-butyl-3-methylimidazolium chloride ([C4 mim]Cl), 1-hexyl-3-methylimidazolium chloride ([C6 mim]Cl), 1-methyl-3-octylimidazolium ([C8 mim]Cl), chloride methylimidazolium ([C10 mim]Cl) and 1-dodecyl-3-methylimidazolium chloride ([C12 mim]Cl). Materials: Aqueous solutions of ILs (2.5, 5, 10, 25 and 50 wt%) were tested with an ASNase concentration of 0.1 mg.mL−1; enzyme activity was measured through the L-aspartic β-hydroxamate acid (AHA) method. Results and discussion: ASNase activity increased in the presence of all ILs at lower concentrations (2.5 wt%). Higher activity values were observed in the presence of ILs presenting more hydrophilic cationic moieties. Activity decreased with the increase in ionic liquid concentration and length of the alkyl chain of the cation. We attributed the decrease in ASNase activity to the IL tensioactive effect on the amino acids sequence of protein, which might have resulted in conformational changes, culminating in ASNase unfolding. In addition, very high concentrations of ILs (25 wt%) resulted in enzyme denaturation by a surfactant-like effect caused by ILs micelles formed. Conclusion: ILs of lower alkyl chains ([C2 mim] Cl and [C4 mim]Cl) at concentrations up to 5 wt% resulted in the best results, with ASNase superactivity. Acknowledgements: FAPESP (grants 2013/08617-7 and 2016/22065-5), CAPES, CNPq and FCT-PT.

AN INNOVATIVE STABILITY-INDICATING UHPLC METHOD FOR DETERMINATION OF MOMETASONE FUROATE IN ITS BULK FORM AND IMPLANTS

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Introduction: Mometasone furoate (MF) is a glucocorticoid with anti-inflammatory activity, used for the treatment of topical skin disorders, rhinitis and mild to moderate persistente asthma. An innovative stability indicating reversed phase Ultra High Performance Liquid Chromatography (RP-UHPLC) method was developed and validated under current International Conference of Harmonisation (ICH) guidance for the determination of mometasone furoate and impurities in active pharmaceutical ingredient (API) and implants. Methods: The best conditions achieved in the method were using an Acquity UPLC® BEH RP-18, 1.7 μm x 2.1 mm column, set to 35 °C with isocratic elution using acetonitrile/water (1:1) (v/v), flow rate equal 0.55 mL.min−1, injection volume of 1μL and wavelength 254nm. The developed method was validated for MF and impurities to ICH recommendations for accuracy, linearity, precision (repeatability), limit of detection, limit of quantitation, robustness and specificity. The selectivity was carried out for MF by forced degradation, employing degrading agents (acid, alkaline, water, metal ions, humidity, heat, light and oxidation agents). Results and discussion: Selectivity of the method was evaluated by spectral purity of mometasone furoate and its related compounds on chromatographic peaks obtained at each condition, from stress testing. Linearity tests showed regression coefficient of 0.9999. For inter-day precision, RSD values were 0.50%. Recovery rates ranged from 99.85 to 101.65%. To evaluate the robustness, fractional factorial design was employed and no significant difference between results was obtained. Conclusions: An innovative UHPLC method for quantification of mometasone furoate and its related compounds were developed and validated, attending requirements established by ANVISA and ICH. Financial Support and acknowledgements: CNPQ, FUNED, CAPES.
DEVELOPMENT OF AN IN VITRO THREE-DIMENSIONAL (3D) MELANOMA MICROENVIRONMENT MODEL USING LIQUID-OVERLAY TECHNIQUE

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Introduction: Melanoma is the most severe type of skin cancer and despite the number of candidates to melanoma antitumor agents is increasing currently, the lack of in vitro models, which include the presence of the tumor microenvironment weakens the process. Three-dimensional (3D) culture is one of the best in vitro models to mimic the tumor microenvironment. Thus, our objective was to develop a 3D model for melanoma, based on cells co-culture to form spheroids.

Methods: Using spheroid formation strategies, a 3D murine melanoma cellular model including B16F10 cell line, macrophages, and fibroblasts was developed. Among the attempts, the model was standardized using agarose gel 2% and a cell density of 1.2×10⁴ well to the spheroid formation. The inflammatory profile associated with the macrophages-containing spheroids was induced using LPS to M1 and dexamethasone to M2 polarization. Following the characterization, spheroids were incubated with dacarbazine and paclitaxel to compare the bi-dimensional (2D) and 3D models.

Results and discussion: Spheroids size was around 300 µm (as found in the literature), showed a rigid form, and an apparent stability, probably due to high extracellular matrix production. Spheroids apparently showed two different regions: a peripheral zone containing viable cells and an internal zone containing necrotic cells which were demonstrated by the decrease in the number of cells on the 7th day when compared with the 4th day, and by the presence of empty spaces inside the spheroids, visualized by microscopy. Additionally, it was observed significant cytotoxic differences between 2D and 3D models for the drugs tested.

Conclusions: we developed a 3D melanoma model to improve the screening of new antitumor agents when compared to a 2D monoculture model.

Financial support: This study was supported by grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina (FAPESC).

DEGRADATION PROFILE OF RI76 – A NEW HYDRAZINE-THIAZOLE DRUG CANDIDATE WITH ANTIFUNGAL ACTIVITY

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Introduction: RI76 is a novel 2-thiazolylhydrazone synthesized in UFMG. It has shown potent in vitro activity against Candida spp., Cryptococcus spp. and Paracoccidioides spp., including higher potency than fluconazole for some of the tested species. The goal with this work is to follow-up the development of this drug candidate by investigating its degradation profile according to current stress testing guidelines. Methods: A synthesized batch of RI76 with ca. 95% purity was submitted to forced degradation conditions listed in IT nº 1/2008 of ANVISA, which are 0.1M HCl, 0.1M NaOH, 0.05M CuSO₄ and 0.3% H₂O₂. The outcomes of these tests were analysed in a stability-indicating method developed on a HPLC-DAD system. Results: RI76 presented intense degradation in aqueous media, with the formation of a single degradation product. After 24h, over 70% of the compound was converted into this product when diluted in water/acetonitrile. This degradation was not detected up to 72h when water was not used as solvent. The use of 0.1M HCl accelerates this degradation, and reacts to form a second minor degradation product. The same was observed for 0.3% H₂O₂, while for 0.1M NaOH and 0.05M CuSO₄, an almost complete degradation is instantly observed, requiring the use of slighter conditions to achieve relevant results. Conclusions: Although RI76 is a strong candidate to antifungal drug in terms of safety and efficacy, it is highly unstable. After characterization, the antifungal activity and safety of the main degradation product will be assessed, to investigate if RI76 may be designed as a prodrug.

Acknowledgments: The authors would like to thank FAPEMIG and CAPES for the Financial Support.
PHASE DIAGRAMS OF PEG/SALT AND PEG/IONIC LIQUIDS FOR THE PURIFICATION OF PROTEIN DRUGS

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Introduction: Aqueous biphasic systems (ABS) are biocompatible alternatives for traditional organic-water solvent extraction that can be used for protein drugs. These systems are mostly composed of water with no volatile organic compounds, turning this purification platform environmental friendly. ABS are formed by a combination of polymers, salts or ionic liquids (ILs), the most common polymer is poly(ethylene glycol) (PEG). PEG is also used to lower the immunogenicity and increase plasma half-life of protein drugs, by means of a covalent attachment known as PEGylation. Methods: The phase diagrams of PEG/citrate and PEG/citrate + imidazolium-based IL ABS were constructed for further application in PEGylated proteins purification. The ILs used were 1-ethyl-3-methylimidazolium triflate (TRIF-IL) and 1-ethyl-3-methylimidazolium dimethylphosphate (DMP-IL) acting as adjuvants in PEG/citrate systems. Results: Phase diagrams were obtained by cloud point titration and show that the molecular weight of PEG have a strong effect in the ability to form a two phase system, with the following trend: PEG 20000 > PEG 10000 > PEG 2000. The effect of PEGmethylation in ABS formation was also evaluated since PEGylation is performed with methyl-PEG. Discussion: The presence of methyl group does not affect the ability to form two phases. Moreover the stability of a model protein L-asparaginase in the IL was investigated and show that protein preserved activity in up to 2.5% of DMP-IL and up to 10% TRIF-IL. Conclusions: The purification of PEGylated proteins (biobetters) through ABS platforms is under investigation for the separation of unreacted proteins from the PEGylated ones.

MINIATURIZED SPECTROPHOTOMETRIC METHOD FOR QUANTIFICATION OF TANNINS IN POMEGRANATE (Punica granatum L.) FRUIT PEEL DRIED EXTRACTS

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Introduction: Punica granatum L. (pomegranate) is one of the oldest edible fruits used for treatment of countless diseases. The bioactivity of this fruit is mainly related to tannins, especially elagitannins. Punica granatum L. fruit peel dried extracts (PPDEs) are widely marketed today and the lack of accessible quality control methods is a key to the variable and questionable quality of these products. To develop a miniaturized spectrophotometric method for quantification of tannins in commercial PPDEs. Methods: Spectrophotometric method using Folin-Ciocalteau reagent was developed and validated for quantification of total polyphenols and polyphenols not adsorbed by hide powder in 17 samples of commercial PPDEs. Tannins content was calculated by the difference between total polyphenols and polyphenols not adsorbed by hide powder in 17 samples of commercial PPDEs. Tannins content was calculated by the difference between total polyphenols and polyphenols not adsorbed by hide powder contents and expressed as pyrogallol. The UV/Visible microplate spectrophotometer was operated at 760 nm. Results and discussion: The developed miniaturized method was precise, accurate, selective and linear, and has no rotational or translational matrix effect. This method significantly reduced the cost of the analysis: 82.2% with reagents, 84.7% in electricity consumption, and 56.3% in the total analysis time. The wide variability in tannins contents in commercial PPDEs. Conclusions: A miniaturized spectrophotometric method was successfully developed and fully validated, being appropriate for quantification of tannins of PPDEs in quality control routine analysis, as it showed to be a simple and cheaper method.
SIMULTANEOUS DETERMINATION OF ANTIHYPERTENSIVE, ANTI-DIABETICS AND ANTILIPEMIC DRUGS BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY TANDEM MASS SPECTROMETRY

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Introduction: It is estimated that 17 million people die each year from cardiovascular diseases around the world. The main causes are arterial hypertension, diabetes and dyslipidemias. Non adherence to pharmacological treatment may cause complications. In order to monitor pharmacological therapy and adherence to treatments, a method to determine 29 drugs in human plasma is proposed. Methods: Ion source parameters, such as gas flow rate, capillary voltage and temperature were optimized employing a solution of the less ionized analyte. The other parameters, such as declustering potential, collision energy, collision cell exit potential and ion transitions were performed for each analyte. Chromatographic separation was carried out on an Agilent Poro- 

shell C18 (150 x 2.1 mm, 4 µm) column. Water, acetonitrile and methanol with different additives were tested as mobile phase. Different gradients were evaluated to optimize chromatographic separation. Scheduled MRM algorithm was employed. Results and discussion: Quantitation and confirmation ions of all 29 analytes were appropriately obtained. The best chromatographic separation was obtained employing 0.1% formic acid in water and 0.1% formic acid in methanol as mobile phase in gradient elution mode. Mobile phase flow-rate was 400 µL/min and column temperature was 30 °C. The total run time was 15 minutes and the chromatographic method allowed appropriate separation of the analytes. Scheduled MRM algorithm provided adequate detectability. Conclusions: The mass spectrometry and chromatographic parameters were optimized, obtaining adequate separation in an acceptable run time. Sample preparation methods will be further evaluated to obtain suitable extraction yields for the drugs from plasma samples.

Financial Support: The authors would like to thank FAPEMIG, CAPES and CNPq.

DEVELOPMENT OF UHPLC METHOD USING FUSED CORE COLUMN FOR QUALITY CONTROL OF COUNTERFEIT AND GENUINE DRUGS CONTAINING SILDENAFIL CITRATE AND/OR TADALAFIL

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Introduction: Phosphodiesterase-5 inhibitors, such as sildenafil citrate (SLD) and tadalafil (TAD), are used to treat erectile dysfunction. They are among the main counterfeit drugs marketed in Brazil. The production and marketing of counterfeit drugs, in addition to being a crime problem, poses a serious threat to public health. In order to determine SLD and TAD simultaneously for quality analysis of counterfeit and genuine drugs, an ultra-high-performance liquid chromatograph (UHPLC) method using fused core column was developed. Methods: UHPLC-UV method was performed using a Phenomenex C18 (50 x 2.1 mm, 1.7 µm) column. For method optimization, different aqueous and organic phases were tested. Different ratios of eluents, oven temperatures and injection volumes were also evaluated. The mobile phase flow-rate was optimized by Van Deemter curves. The linearity of the optimized method was evaluated at nine concentration levels, corresponding to 20-180% of the working concentrations (70 µg/ml for SLD and 20 µg/ml for TAD). Results: The best chromatographic parameters were obtained with a column maintained at 30 °C and the mobile phase was composed of acetonitrile and 0.1% aqueous triethylamine, pH 3.0 adjusted with formic acid (35:65, v/v), at a flow-rate of 0.3 ml/min. UV detection was performed at 290 nm and the injection volume was 2 µl. The running time was 2.5 minutes. The calibration curve was linear in the range evaluated. Conclusions: A simple and linear UHPLC method for the simultaneous quantification of SLD and TAD was developed. Subsequently, method will be validated and applied in quality control of tablets.

Financial Support: The authors would like to thank FAPEMIG for the financial support.
DEVELOPMENT AND VALIDATION OF AN LC-PDA METHOD FOR THE SIMULTANEOUS QUANTIFICATION OF NAPROXEN SODIUM AND SUMATRIPTAN SUCCINATE IN ASSAY, SOLUBILITY AND DISSOLUTION TESTS

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Introduction: Migraine is a neurovascular disorder that is characterized by pulsating headache. The association of naproxen sodium (NAP) – acidic drug a non-steroidal anti-inflammatory – and sumatriptan succinate (SUM) – a basic drug selective 5-hydroxytryptamine-1 receptor agonist – is used for the treatment of migraine attacks. Therefore, it is difficult to establish methods for simultaneous determination of these drugs. Methods: The HPLC-PDA method was developed and validated for simultaneous quantification of NAP and SUM. HPLC separation was performed on an cyano column (150 × 4.6 mm i.d.; particle size 5 µm) maintained at 30 °C. The mobile phase consisting of 4 mM aqueous ammonium acetate pH 4.90, adjusted with glacial acetic acid, and acetonitrile (64:36, v/v) delivered at a flow rate of 1 mL min⁻¹. The sample was maintained at 8 °C and the injection volume as 5 µL. Method validation was performed according to methods described in the following regulatory guidance documents. Results and discussion: The developed HPLC-PDA method was linear, precise and accurate over the ranges of 7.5 a 14.5 µg mL⁻¹ for NAP and 0.1 a 3.25 µg mL⁻¹ for SUM. The method was selective in buffer media with pH 1.2; 4.5; 6.8 and 7.5. The running time was 6 minutes with a resolution of 3.38 between the peaks corresponding to NAP and SUM. Conclusions: The HPLC-PDA method was successfully developed and fully validated being appropriate for simultaneous quantification of naproxen sodium and sumatriptan succinate in quality control routine analysis of assay, solubility and dissolution of tablets containing such drugs.

DETERMINATION OF GLICLAZIDE USING MOLECULARLY IMPRINTED SOLID-PHASE EXTRACTION AND HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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Introduction: Gliclazide is a hypoglycemic drug used to treat diabetes mellitus type 2 and its determination is required in drug development and therapeutic monitoring. It is usually extracted from biological samples using conventional techniques. In this context, this study aims to develop method to determine gliclazide employing molecularly imprinted solid-phase extraction (MISPE), a novel technique with high selectivity to the analyte, and liquid chromatography (LC). Methods: Synthesis of molecularly imprinted polymer (MIP) was carried out by precipitation polymerization using gliclazide as template. Different combinations of functional monomers, crosslinkers and porogen solvents were tested. After template removal, MIPs were packed in cartridges and applied as sorbent in solid-phase extraction (SPE) of gliclazide from aqueous samples. Thermal analysis and electronic microscopy were used for MIP characterization. LC method with ultraviolet detection at 230 nm was developed for determination of gliclazide using a Poroshell C18 (100 x 4.6 mm, 4 µm) column. Results and discussion: The best MIP synthesis condition, regarding reaction yield, distribution coefficient and selectivity, was obtained with 2-hidroxietilmethacrylate, ethylene glycol dimethacrylate, acetonitrile and 2,2'-azobisisobutironitrile. Gliclazide concentration, sample pH and solvent proportion affected drug recovery from aqueous samples. Thermal analysis and electronic microscopy demonstrated that MIP has suitable properties to be used as SPE sorbent. LC method allowed appropriate determination of gliclazide in only four minutes. Conclusions: The MIP synthesized presented selectivity and high extraction capacity of gliclazide. MISPE-LC method was able to determine gliclazide in aqueous samples. Application of MIP for gliclazide extraction from human plasma is currently in progress.

Financial support: The authors would like to thank CAPES for the financial support.
IDENTIFICATION OF PHENOLIC COMPOUNDS IN BLACKBERRY (Rubus sp) CULTIVAR ‘XAVANTE’ BY UPLC-QTOF-MSE

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Introduction: Blackberry, a fruit belonging to the Rosacea family, is rich in phenolic compounds and therefore a source of natural antioxidants. Their effectiveness in prevent the deterioration of oxidizable products such as cosmetics and food products, make the blackberry a viable alternative to synthetic antioxidants, consequently having an impact in human health. Thus, the identification of the phenolic compounds present in the blackberry cv. ‘Xavante’ is essential to relate its high antioxidant activity and to the best of our knowledge there is a lack of information about the compounds presents of this cultivar.

Methods: Analyzes were performed using an Waters UPLC Acquity H-Class system coupled to Xevo G2-S Quadrupole Time-of-Flight Mass Spectrometer, provided with electrospray ionization source and operated in the both ionization mode. The peaks were identified with the reference standards or were deduced by the mass accuracy.

Results and discussion: The analysis in the UPLC-QTOF-MS revealed the presence of cyanidin (m/z 287.0556); cyanidin hexoside (m/z 449.1076); cyanidin-malonyl hexoside (m/z 535,1076), in positive mode; o-hexosyl-deoxyhexosyl quercentin (m/z 609.1449); ellagic acid (m/z 300,9981); citric acid (m/z 191,0196); quercetin (m/z 301,0340); catechin (m/z 289,0709); epicatechin (m/z 289,0707), in negative mode. These compounds had antioxidant activity reported in the literature, evidencing that there is application of cv ‘Xavante’ for studies that prove beneficial effects for human health.

Conclusion: More research is needed to understand metabolism and the bioavailability of blackberry’s phenolic compounds and how they may confer health benefits.

INVESTIGATION OF DEGRADATION PRODUCTS OF DASABUVIR UNDER ALKALINE STRESS CONDITION BY UPLC-QTOF-MS

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Introduction: Dasabuvir (DBV) is an antiviral drug that acts by inhibiting the hepatitis C Virus replication. Efficacy and safety of the medicines are related to stability, since the appearance of degradation products (DP) implies subtherapeutical doses and/or toxic products, therefore compromising the pharmacotherapy. The elucidation of DP’s structure is an important step to fulfill quality control requirements, since the structure is necessary to synthetize the standards, allowing the quantitation of those substances in the final product and the elucidation of the formation mechanism to control these variables during the production process. This study proposes investigating the structure of DBV’s degradation products, since they have not yet been reported.

Methods: DBV was undergone to stress degradation in alkaline conditions (pH 13 and 14). The separation and detection was performed using an UPLC-qTOF-MS system (Waters, Acquity H-Class), Acquity UPLC-BEH C18 column (2.1x100mm, 1.7µm) with mobile phase formic acid 0.1% - acetonitrile (55:45, v/v) at a flow rate of 0.4mL/min. The ESI (both positive and negative) parameters were: Cone voltage 50V; capillary voltage -3 to +2kV; source offset: 80V; source temperature: 150°C; dessolvatation gas: 400°C. The mass range was 100-600 Da and the acquisition time was 5 min.

Results and discussion: DBV was susceptible to alkaline medium. As result of MS analysis at low and high energy by exact mass (error

Conclusions: DBV and its DPs were detected, being possible to propose two new degradation products structures.
DEVELOPMENT OF RP-HPLC-DAD METHOD FOR SIMULTANEOUS DETERMINATION OF DASABUVIR AND RELATED SUBSTANCES

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Introduction: Dasabuvir (DBV) is an antiviral drug used to treat hepatitis C Virus (HCV) infection. It works by inhibiting NS5B polymerase, which is responsible for the viral replication. Since efficacy and safety of the medicines are related to their stability, the presence of degradation products may compromise the therapeutic effect and, in some cases, the occurrence or increase of adverse effects, which makes the stability evaluation a crucial parameter of quality. To the best of our knowledge, no LC methods capable of detecting DBV and its degradation products has been reported. Thus, this study proposes to develop a LC-DAD method for this purpose. Methods: DBV underwent stress degradation conditions, such as acidic, alkaline, oxidative, photolytic and thermal. The chromatographic development was performed using an LC-DAD system (Agilent 1100 series), by testing different conditions (columns, mobile phase compositions, buffers, flow rates, temperature and wavelength detection). Results and discussion: DBV was shown to be sensitive to acidic and alkaline medium, while stable to oxidative, photolytic and thermal conditions. The optimal separation was achieved using a Symmetry® C18 (4.6x75mm, 3.5µm) column and formic acid 0.1% - acetonitrile (55:45, v/v) as mobile phase, at a flow rate of 1 ml/min. The analytes were detected at 254nm. Conclusions: DBV and its degradation products were properly separated and the method developed was selective for detection of DBV in the presence of its degradations products and impurities. Therefore, the method is suitable for use in stability studies and for quality control purposes.

OPTIMIZATION, VALIDATION AND APPLICATION OF UV SPECTROPHOTOMETRIC METHOD FOR QUANTIFICATION OF AMLODIPINE BESYLATE IN TABLETS DISSOLUTION TEST

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Introduction: Amlodipine besylate (AMB), a calcium channel blocker, is used in the treatment of hypertension and angina. There is no monograph for AMB tablets in the Brazilian Pharmacopoeia. Therefore, for the quality control of AMB tablets batches, The United States Pharmacopoeia 40 ed (USP 40) is used. However, the dissolution analytical method is not selective for tablets marketed in Brazil, since the excipients used in Brazilian formulations show significant absorption at the 239 nm wavelength recommended in the USP 40 method, thus interfering in the quantification of AMB and so, the analytical method has to be optimized and validated. Methods: For method optimization, different detection wavelengths were tested. The method was validated according to the literature and current legislation. Then, samples of generic, reference and similar tablets were subjected to the dissolution test using paddle apparatus at 75 rpm and 500 mL of 0.01 M hydrochloric acid at 37.0±0.1 °C as dissolution medium. 10 mL samples were withdrawn after 30 min, immediately filtered and analyzed employing the optimized and validated ultraviolet absorption spectrophotometry method. Results: In the optimized analytical method the diluent consisted of 0.01 M hydrochloric acid and detection was performed at 366 nm. Regarding the linearity of the analytical method, the residuals presented random distribution and the method proved to be linear in the range of 8.4 to 19.6 µg/mL. The relative standard deviation (RSD) obtained in the intra-day and in inter-days precision were lower than 2.0%. Concerning of the method accuracy, all average recoveries were within the specified limits, between 98.0 and 102.0%. The method proved to be selective, so that the quantification of the AMB is not influenced by the tablet excipients and the method was robust. The validated method was applied to determine AMB in dissolution test of three batches of the drug. The evaluated batches were considered adequate at the dissolution test, since quantities of AMB dissolved from the tablets tested were in accordance with the pharmacopoeial specification. Conclusions: A simple and selective ultraviolet absorption spectrophotometry method was optimized and validated for tablets containing AMB marketed in Brazil. The method will be submitted to the Brazilian Pharmacopoeia Commission for publication in future editions of this compendium.

The authors would like to thank CNPq for the financial support.
A VALIDATED METHOD BY HPLC-MS/MS FOR THE SIMULTANEOUS DETERMINATION OF CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN AND METFORMIN

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Introduction: The combination of metformin with sodium-glucose-cotransporter-2 inhibitors (iSGLT2) is recommended when lifestyle modification alone and monotherapy does not reduce glycemia. In order to enable pharmacokinetic studies, this study aims to validate a method for simultaneous quantification of metformin and iSGLT2 (canagliflozin, dapagliflozin empagliflozin) in plasma. Methods: After one-step protein precipitation of plasma using acetonitrile with 0.1% formic acid, analyses were performed using an Agilent 1200 HPLC System coupled to an Applied Biosystems API 3200 Triple Quadrupole MS operating in ESI positive ion mode. Chromatographic separation was obtained in an Xbridge C18 column (50 x 2.1 mm, 5 µm), maintained at 35°C, and a guard-column of the same material. The mobile phase consisted of acetonitrile:water (both containing 1 mM ammonium formate and 0.1% formic acid) in gradient mode. The flow rate, injection volume and total run time were 0.2 mL.min⁻¹, 20 μL and 9 minutes, respectively. The method was validated according to Anvisa and FDA guidelines. Results and discussion: The method achieved great sensitivity and showed suitable coefficients of correlation (r⁻¹ for canagliflozin and metformin, 10⁻⁴⁻⁰⁰ ng.mL⁻¹ for dapagliflozin, and 15⁻¹⁰⁻⁰⁰ ng.mL⁻¹ for empagliflozin. Satisfactory recoveries were achieved for compounds, with adequate reproducibility (RSD). Conclusion: The method demonstrated to be applicable for pharmacokinetic studies.

THE PRESENCE OF DRUGS OF ABUSE IN SURFACE WATER FROM CURITIBA-PR (BRAZIL): A SNAPSHOT

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Introduction: Several studies have reported the occurrence of drugs of abuse in the environment. Hence, to our knowledge, this is the first comprehensive study to specifically address the contamination of Belém river in Curitiba, Brazil. The aim of this preliminary study is to achieve the simultaneous identification of targeted compounds in surface water using LC-QTOF-MS. Methods: Surface waters samples were collected from the river in February 2018. Strata-X® cartridges were used in the extraction procedure. The analysis were conducted on an Acquity UPLC H-Class system coupled with a Waters Xevo G2-S QToF mass spectrometer. The method was applied for identification of popular drugs of abuse, their metabolites and drugs commonly added in cocaine as adulterants. Analytes and their metabolites were confirmed by mass accuracy (error less than 5 ppm), and through tandem mass spectrometry fragmentations. Results and discussion: Through mass accuracy and fragments the following compounds were identified in samples: benzoylcegonine, cocaine, anhydroecgonine, ecgonine methyl ester, norcocaine MBDM and codeine. In addition, the adulterants lindocaine, phenacetin and caffeine were also found. High resolution mass spectrometry supported by the creation of a target compound list with retention time data allowed a rapid, selective and specific screening of compounds in these environmental samples. Conclusion: The method was successfully applied for a comprehensive screening with simultaneous determination of drugs of abuse and their metabolites and adulterants. Acknowledgments: We gratefully acknowledge to Federal University of Paraná (UFPR) and the financial support of Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).
INVESTIGATION OF NON DECLARED CHEMICAL SUBSTANCES IN PRODUCTS MARKETED AS HERBAL MEDICINES

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Introduction: Herbal medicines have a historical basis for their uses. There is a high demand for herbal products and, in this scenario, drug falsification is a concern and brings risks to consumer’s health. In order to continue the studies carried out by the Pharmaceutical and Medicinal Chemistry research group at UFSC, three different capsules labeled and sold as natural products were investigated to identify the presence of possible synthetic drugs. Next, their labels were also verified regarding the quality of the contained information. Methods: The chemical analysis was realized through partitioning and chromatographic methods for extraction and isolation of compounds. 1H NMR and mass spectrometry (ESI-TOF) were used for chemical characterization. The analysis of label information was made through legislation publicized by ANVISA. Results and discussion: The chemical analysis aided by TLC, NMR and MS allowed us to isolate and identify furosemide as an undeclared synthetic substance in one of the analyzed products - marketed for “weight loss”. The information contained in the labels of products investigated infringed current ANVISA regulations, leading customers to misinterpretation and endangering their health. Conclusions: Our methods allowed the identification of furosemide as an undeclared synthetic substance in one of the products. These products could be classified as a threat to public health once the consumers would not be aware of dosage, drug-drug interactions, or possible side effects. Acknowledgments: We would like to thank CAPES, CNPq and PPGFAR/UFSC for financial support.

PRELIMINARY STUDIES OF FORCED DEGRADATION FOR THE DEVELOPMENT OF A STABILITY-INDICATING HPLC METHOD FOR BENZNIDAZOLE

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Introduction: Benznidazole is used for treatment of Chagas disease, which is considered by WHO a neglected disease. At the present moment, there are no stability-indicating methods described in the literature and little is known about its degradation pathways. The aim of this study was to conduct forced degradation studies on benznidazole and to develop a stability-indicating method for this drug. Methods: Based on ICH Q1A, RDC 53/2015 guidelines and technical literature, acidic, alkaline and neutral hydrolysis, as well as oxidative conditions were tested to investigate benznidazole’s degradation profile. For the development of the stability-indicating method, degrading agents, stressed and unstressed benznidazole samples were injected on a HPLC-DAD system equipped with an Agilent HC-C18 (150 x 4.6 mm, 5 µm) column. Results: Benznidazole peak area decreased under alkaline conditions. When stressed with 0.1 M NaOH at 40 °C, after 8h, a degradation of over 10% was achieved. Chromatographic peaks, unrelated to the blank, could be observed on the chromatogram, indicating the formation of degradation products. Under acidic conditions, using 1 M HCl at 70 °C, after 7 days, a small degradation product peak was detected. However, no significant peak size decrease was observed for benznidazole. No degradation was observed under oxidative stress, using 3% H₂O₂ at room temperature and 0.05 M CuSO₄ at 40 °C for 3 days. Conclusion: The results showed that benznidazole is sensitive to alkaline pH and slightly sensitive to acidic pH. Using the obtained data, a stability-indicating method to separate benznidazole and its degradation products is in progress. The authors would like to thank CAPES for the financial support and LAFEPE for donating the active pharmaceutical ingredient and tablets used in this study.
QUALITY ASSESSMENT OF METFORMIN HYDROCHLORIDE TABLETS COMMERCIALLY AVAILABLE AT BRAZIL

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Introduction: Metformin hydrochloride (MET) is considered the main oral hypoglycemic medication for the treatment of diabetes mellitus II (DM2), and it’s present in the national market through different brands and immediate release solid oral dosage forms. This study is justified by the need to conduct the quality control of these drugs that are widely used by the population, and easily accessible in drugstores.

Methods: Specialty pharmaceuticals were evaluated as MET coated tablets at 500 mg and 850 mg dosages: two reference medicines (R1, R2) and six generic medicines (G1 - G6), summing up eight samples. The products were analyzed by the assays described in the monograph, Metformin Hydrochloride Tablets, of Brazilian Pharmacopeia (FB5), which were weight variation, hardness, disintegration, dissolution and uniformity of dosage units.

Results and discussion: All 850 mg MET (4/4 = 100%) tablets were approved in all tests. However, we found 25% disapproval among laboratories (1/4) that produced 500 mg MET tablets. It should be pointed out that quality deviations must be identified and eliminated throughout the production process to assure the total quality related to the benefit of the pharmacotherapeutic treatment.

Conclusions: Effective health surveillance policies should be adopted to check the quality of generic medicines marketed in Brazil. Financial support: PROPE-UFSJ.

STUDIES OF THE DISSOLUTION AND LIBERATION PROFILE OF THE ISOFLAVONES CONTAINED IN SOFT GELATIN CAPSULES CONTAINING SOYBEAN GERMEN (Glycine max L. Merril)

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Introduction: Isoflavones, contained in soybeans, are flavonoids that resemble estrogen and present 12 different chemical forms. It has effects for the treatment and prevention of heart disease, cancers of the colon, breast, prostate and osteoporosis, besides causing relief of the menopausal symptoms. Methods: The mean weight, loss by desiccation, total ash content and disintegration of the capsules was performed according to [1], the total flavonoids dosage was assayed according to [2], and the dissolution and liberation profile of isoflavones from soybean germ capsules was performed according to [1]. Results and discussion: Capsule characterization was performed based on the determination of the mean weight of 549 mg, loss of desiccation 6.1921 g/100 g, determination of ash content 3%, and disintegration time of 12 minutes in medium with HCl. The total flavonoid content was 164 mg/100g. The chromatographic profile of the soybean germ by HPLC-UV, genistein and genistin were identified by comparing the retention time and co-injection of the sample enriched with the standards, obtaining retention times of 5.876 min and 6.427 min respectively. Applying the equation of the straight line of the calibration curve, the genistin concentration estimate was 1013.31 μg/mL. For the dissolution profile of the capsules, simulated gastric fluid pH 1.2 was used, carried out in a time of 1 hour, at intervals of 5 minutes, and collecting aliquots of 5 mL, where liberation of genistin was observed. Conclusion: The soft gelatin capsules containing soybean germs met all criteria of the Brazilian pharmacopoeia.

Section
Biological Assays, Biomarkers and Diagnostics
ASSOCIATION BETWEEN HPV AND BACTERIAL VAGINOSIS SUGGESTS A SINERGISTIC ACTION ON THE PROGRESSION OF CERVICAL LESIONS

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The link between high-risk human Papillomavirus (hrHPV) and bacterial vaginosis agents on the development of cervical lesions and cancer is still unclear. Thus, we investigated the rates of co-infections between HPV and thirteen key markers of bacterial vaginosis (KM-BV) in different cervical findings. A total of 213 women were screened using Papanicolaou smears for cervical abnormalities, HPV and KM-BV using single PCR (S-PCR) and multiplex-PCR (M-PCR) (CONEP n° 085/2011 and 104/2012). A total of 130 (61%) women exhibited abnormal cytology (≥ LSIL). HPV-DNA prevalence was 69.9%, and HPV-16 was the most prevalent type in women with NILM and ≥ LSIL cytology. KM-BVs were detected in 72.7% women as single agent (34.7%) or in association (n=81, 38%). It was possible to detect that, co-infections between KM-BV + HPV-DNA and hrHPV increased the risk for ≥ LSIL and to HSIL plus squamous cervical cancer (SCC). The most frequent KM-BV detected was Gardnerella vaginalis (33.8%), followed by Megasphaera type I (22.5%). Co-infections between G. vaginalis with HPV-DNA and hrHPV increased four times the risk for ≥ LSIL cytology and to HSIL plus SCC. Co-infections M. type I with hrHPV increased five times the risk for ≥ LSIL cytology and to HSIL plus SCC. These two KM-BVs were the primary pathogens associated with hrHPV on the increased risk for all grades of cervical abnormalities but mainly for HSIL plus SCC, suggesting a possible synergistic action on the progression of cervical lesions. Our results reinforce the hypothesis that some KM-BV might play a role as co-factors in HPV-mediated cervical carcinogenesis.

Financial Support: This work was supported by grants from Brazilian Government (PROCAD 88881.068413/2014-01).

PARTICULATE MATTER (PM10) INDUCES SKIN BARRIER DYSFUNCTION AND WATER TRANSPORT IN A RECONSTRUCTED HUMAN EPIDERMIS MODEL

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Introduction: Environmental pollution is a major concern worldwide, specifically, air pollution by particulate matter (PM) that has been linked to the development of many diseases e.g. atopic dermatitis. The development of in vitro models that reproduce the normal epidermis is of great value to study pathophysiological processes of the skin. The objective of this study was to investigate the alterations induced by the exposure of a Reconstructed Human Epidermis (RHE) to PM10 in proteins of differentiation and water transport of the skin. Methods: The RHE was exposed to 2.2, 8.9 and 17.9 µg/cm² of a standard Urban Particulate Matter (NIST SRM 1648a) for 24 and 48 hours. Immunohistochemistry detection of epidermal markers was based on the streptavidin-biotin technique for the proteins of epidermis differentiation cytokeratin 10, involucrin, loricrin, filaggrin, and the transmembrane protein aquaporin 3. Results and discussion: Cytokeratin 10 indicates the good stratification of the RHE however reduced expression was observed after the treatment with the two highest doses, as with filaggrin, involucrin and loricrin. Aquaporin 3 was increased in RHE exposed to PM10 in comparison to control. This last observation can lead to increased water transport to the stratum corneum contributing to water loss and dry skin as observed in atopic eczema. Conclusion: Exposure of a RHE to PM10 induces dose dependent alterations in the epidermis with loss of proteins at granular and cornified layers and increased aquaporin 3 suggesting alterations of barrier function and water transport across the epidermis with possible epidermis dehydration.

Ethical approval: CAAE 0062.0.198.000-09
ONCOSTATIN M RECEPTOR: POSSIBLE BIOMARKER FOR SYSTEMIC SCLEROSIS?

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Introduction: Systemic Sclerosis (SSc) is an autoimmune disease characterized by vascular damage, immunological dysregulation and fibrosis of the skin and internal organs. SSc presents dysregulated production of cytokines and their receptors that are involved in vascular damage and fibrosis. Oncostatin M (OSM) is a cytokine produced by activated T cells, monocytes and macrophages that perform functions in fibrotic process, such as increased collagen production and differentiation induction of myofibroblasts. This cytokine performs its functions through the signaling in its receptors. The type II receptor called OSM-R is more specific and performs a greater number of functions by binding to OSM. The objective of this study was to evaluate serum levels of OSM-R in patients with systemic sclerosis and healthy controls and its association with clinical manifestations.

Material and methods: Sixty SSc patients (mean age 45.57 ± 12.10) and sixty controls (mean age 56.28 ± 14.49) were assessed. Clinical and laboratory parameters were recorded. OSM-R levels were measured by enzyme-linked immunosorbent assay (ELISA) and results were assessed by Student’s “t” test and Spearman’s correlation test. Results: OSM-R serum levels were significantly increased in SSc patients compared with controls (mean 391.886 and 239.779, p. Conclusion: These findings show a significant increase in serum OSM-R levels in SSc patients when compared to controls, and suggest a possible association between serum levels of OSM-R and extent of cutaneous involvement and body mass index in patients with systemic sclerosis.

PARTICULATE MATTER (PM10) INDUCES SKIN BARRIER DYSFUNCTION AND WATER TRANSPORT IN A RECONSTRUCTED HUMAN EPIDERMIS MODEL

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Introduction: Environmental pollution is a major concern worldwide, specifically, air pollution by particulate matter (PM) that has been linked to the development of many diseases e.g. atopic dermatitis. The development of in vitro models that reproduce the normal epidermis is of great value to study pathophysiological processes of the skin. The objective of this study was to investigate the alterations induced by the exposure of a Reconstructed Human Epidermis (RHE) to PM10 in proteins of differentiation and water transport of the skin. Methods: The RHE was exposed to 2.2, 8.9 and 17.9 ug/cm² of a standard Urban Particulate Matter (NIST SRM 1648a) for 24 and 48 hours. Immunohistochemistry detection of epidermal markers was based on the streptavidin-biotin technique for the proteins of epidermis differentiation cytokeratin 10, involucrin, loricrin, filaggrin, and the transmembrane protein aquaporin 3. Results and discussion: Cytokeratin 10 indicates the good stratification of the RHE however reduced expression was observed after the treatment with the two highest doses, as with filaggrin, involucrin and loricrin. Aquaporin 3 was increased in RHE exposed to PM10 in comparison to control. This last observation can lead to increased water transport to the stratum corneum contributing to water loss and dry skin as observed in atopic eczema. Conclusion: Exposure of a RHE to PM10 induces dose dependent alterations in the epidermis with loss of proteins at granular and cornified layers and increased aquaporin 3 suggesting alterations of barrier function and water transport across the epidermis with possible epidermis dehydration.

Ethical approval: CAAE 0062.0.198.000-09
SIN3B: POSSIBLE ROLE IN MELANOMA RESISTANCE AND PROGRESSION

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Introduction: Cutaneous melanoma accounts for the majority of skin cancer deaths, owing to its aggressiveness and resistance to targeted therapies, primarily due to the presence of phenotypic and genetic heterogeneity. Thus, there is a dire need to identify new biomarkers of therapy resistance in melanoma, which can aid the development of new therapeutic strategies. SIN3B scaffolding protein has been shown to have an implication in cancer progression. However, the mechanisms underlying SIN3B role in melanoma is currently unknown. Therefore, this study aims to characterize SIN3B molecular function and regulation during melanoma progression and therapy resistance.

Methods: Expression levels of SIN3B, including its splicing variants, were assessed in a panel of BRAF inhibitor (BRAFi) resistant and sensitive human melanoma cell lines, by qPCR and Western Blotting. Additionally, in silico screenings were performed using TCGA and GEO databases.

Results and discussion: We observed increasing expression of SIN3B during melanoma progression. BRAF-mutant metastatic melanoma cell lines displayed the highest expression values and, a significant decrease in SIN3B levels was observed in BRAFi-resistant cells. Interestingly, qPCR expression analysis showed differences in the expression of SIN3B transcripts in melanoma cell lines, where the predicted isoforms, containing paired amphipatic helix (PAH) domains, showed higher expression values. Conclusions: These results suggest that SIN3B plays a role in melanoma progression and BRAFi resistance. Further understanding of the functional consequences of the expression of different SIN3B isoforms is needed to help elucidate the mechanisms by which SIN3B may contribute to the malignant phenotype of melanoma.

INHIBITION ACTIVITY OF EXTRACT AND FRACTIONS FROM Passiflora manicata LEAVES ON INTESTINAL ENZYMES (α-AMYLASE, α-GLUCOSIDASE AND PANCREATIC LIPASE)

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Introduction: The Andean region of Colombia is considered a dispersion center for many species of the genus Passiflora (Passifloraceae). P. manicata, popularly known as ‘curuba-de-monte’, is one of these species, for which there are few chemical and pharmacological studies. The objective of the present study was to analyze the potential inhibitory activity of the aqueous leaf extract and its fractions of P. manicata on digestive enzymes α-amylase, α-glucosidase and pancreatic lipase. Methods: Leaves of P. manicata were collected in Villa de Leyva, Boyacá, Colombia. The dry leaves was powdered and extracted by infusion (plant:water, 1:10, 95°C) for 10 min, filtered and lyophilized. The crude extract was then fractionated by liquid-liquid partition, giving ethyl acetate, butanol and aqueous fractions. The chromatographic fingerprints were established by TLC and Total Phenolic Content (TPC) was determined by Folin-Ciocalteu method. Determination of IC50 for α-amylase, α-glucosidase and pancreatic lipase was performed for the extract fractions according methodologies previously reported (Lévuok, 2016; Rey, 2015). Results and discussion: The TLC analysis allowed observing a predominance of two main flavonoids, especially in the butanolic fraction, identified as isovitexin and isoorientin when compared to references substances. The TPC, expressed in galic acid equivalents, was higher for butanolic fraction. The best inhibitions effects were also observed for the butanolic fraction, for α-amylase and pancreatic lipase. No sample showed inhibition of α-glucosidase. Conclusion: Butanolic fraction obtained from the aqueous leaf extract of P. manicata showed a promising inhibition of α-amylase and pancreatic lipase enzymes. Further in vivo studies are undergoing. Lévuok KP. Trabajo de Grado de Maestría en Ciencias Biológicas. Pontificia Universidad Javeriana. Colombia; 2016. Rey DP. Rev. Colomb. Cienc Quim Farm. 2015;44(1):27-89.

Financial support: Pontificia Universidad Javeriana – Project #7166
ANNEXIN A1 IN MURINE EXPERIMENTAL COLITIS

INTRODUCTION: Infliximab (IFX) is an anti-TNF-α therapy to inflammatory bowel diseases. Despite IFX efficacy, side effects and non-responsiveness are still reported. IFX modulates annexin A1 (AnxA1), an anti-inflammatory protein involved in intestinal homeostasis. In turn, AnxA1 may possibly mediate IFX effects. Methods: Male C57BL6 wild-type (WT) and AnxA1-deficient (AnxA1-/-) mice received 2% of dextran sulphate sodium (DSS) in drinking water at Days 0, 2 and 4. Inflamed animals were treated intraperitoneally (i.p.) with either IFX, Boc-2 (formyl-peptide receptors - FPRs - pan-blocker) or IFX+Boc-2. Control group received water without additives and vehicle injections i.p. At Day 6, DSS was withdraw, mice were monitored until Day 10 and euthanized to collect colon samples (CEUA/USP nº540). Results/Discussion: IFX prevents body weight loss, decreases fecal blood and disease activity index (DAI) after DSS withdraw in WT mice. DAI and diarrhea are intensified after FPRs blockade. Histopathologically, IFX protects the colonic morphology only in WT. With FPRs blockade, this protection is partially abrogated. AnxA1 expression is increased in damaged epithelial areas from WT/DSS and WT/DSS+Boc-2, but is downregulated in WT/DSS transmigrated leukocytes. In WT/ DSS+IFX mice, epithelial AnxA1 is similar to basal and in leukocytes, this expression is increased, indicating a more advanced resolution. AnxA1-/- mice are more susceptible to colitis and do not respond to IFX therapy, displaying markedly increased TNF-α tissue secretion, aggravated clinical and histological conditions, reduced T regulatory cells and a mortality of 50% compared to WT. Conclusions: AnxA1 signaling through FPRs influences IFX efficacy in protecting mice against DSS-induced colitis.


WATER QUALITY IN THE MUNICIPALITY OF SÃO MATEUS: MICROBIOLOGICAL AND PHYSICOCHEMICAL ANALYSIS

INTRODUCTION: Water is an essential resource for human life, since 75% of the human body is made up of this element, participating in various reactions of living organisms. Considering that the preservation of the quality of this resource is fundamental for the health of the population, the present study sought to evaluate the knowledge of the population about the maintenance of the domestic water reservoirs, besides verifying the quality of the water consumed by the population, mainly the effects of the reservoirs in the physico-chemical and microbiological characteristics of water, in the city of São Mateus, northern region of Espírito Santo. Methods: The collection of socioeconomic data was done through an interview with the residents. For the microbiological analysis, the substrate technique was used, which allows simultaneous detection and identification of total coliforms and E. coli. The results were evaluated using descriptive and inferential statistical tools. This work was submitted and approved by the ethics committee of CEUNES/UFES (Report No. 1,998,738). Results and discussion: The results showed that all the interviewees were aware of the need to clean the water tank, but in 14.29% (n=10) of the households the cleaning was not performed. Regarding the period of cleaning of the water tank, 55.71% (n=39) of the residents perform the cleaning in the correct period. The results of the microbiological analysis of the water show that the samples from the domestic reservoirs were more contaminated than those of the public supply network, with a significant difference (p=0.008) between the groups, for contamination by total coliforms. Considering the free residual chlorine content, of the 166 analyzed samples, 94.58% (n=157) had levels below the recommended for disinfection of the water, and in no sample from the domestic reservoir the minimum content was reached. The high degree of microbiological contamination of the two groups may be directly associated to the reduced residual chlorine content of the samples, especially those from the domestic reservoirs. Conclusions: The use of the domestic reservoir had a negative effect on the quality of the water, both in relation to free residual chlorine contents and contamination by total coliforms, which could cause harm to the health of the population.
**Introduction:** Prostate cancer is the second cause of death due to neoplasms among the men and most frequent non-cutaneous cancer among Brazilians. Recently, several studies have been shown the antitumor potential of bioactive compounds extracted from the plants for treatment of prostate cancer. Carvacrol, a phenolic monoterpene, gained great interest in its antitumor activities. However, its application is still limited due to low solubility and high volatility. In order to improve the hydrophilic and pharmacological properties of carvacrol were prepared inclusion complexes with β-cyclodextrin by different methods. **Methods:** The characterization was evaluated by thermal analysis (DSC and TGA), infrared spectroscopy (FTIR), X-ray diffraction, nuclear magnetic resonance (NMR), scanning electron microscopy (SEM) and entrapment efficiency (EE%). The antitumor effect of carvacrol/β-cyclodextrin inclusion complexes against prostate cancer cells (PC3) was assessed by bi and 3-dimensional cell culture models (2D and 3D). **Results and Discussion:** Results of physicochemical characterization indicated that carvacrol was successfully complexed within β-cyclodextrin cavity. The formation of inclusion complex by freeze-drying method showed highest EE (81.2%). Cell proliferation and migration assays in 2D model demonstrated that treatment of PC3 cells with carvacrol/β-cyclodextrin inclusion complexes led to dose-dependent inhibition of tumor cell proliferation and further reduction of cell viability compared with free carvacrol. In addition, carvacrol/β-cyclodextrin inclusion complexes significantly reduced cell migration. Thus, carvacrol in β-cyclodextrin demonstrated a potential antiproliferative effect, representing a promising alternative in the treatment of prostate cancer. **Acknowledgments:** CAPES, CNPq, FINEP and FAPITEC/SE for the financial support and fellowships.

**Conclusion:** Prostate cancer is the second cause of death due to neoplasms among the men and most frequent non-cutaneous cancer among Brazilians. Recently, several studies have been shown the antitumor potential of bioactive compounds extracted from the plants for treatment of prostate cancer. Carvacrol, a phenolic monoterpene, gained great interest in its antitumor activities. However, its application is still limited due to low solubility and high volatility. In order to improve the hydrophilic and pharmacological properties of carvacrol were prepared inclusion complexes with β-cyclodextrin by different methods. **Methods:** The characterization was evaluated by thermal analysis (DSC and TGA), infrared spectroscopy (FTIR), X-ray diffraction, nuclear magnetic resonance (NMR), scanning electron microscopy (SEM) and entrapment efficiency (EE%). The antitumor effect of carvacrol/β-cyclodextrin inclusion complexes against prostate cancer cells (PC3) was assessed by bi and 3-dimensional cell culture models (2D and 3D). **Results and Discussion:** Results of physicochemical characterization indicated that carvacrol was successfully complexed within β-cyclodextrin cavity. The formation of inclusion complex by freeze-drying method showed highest EE (81.2%). Cell proliferation and migration assays in 2D model demonstrated that treatment of PC3 cells with carvacrol/β-cyclodextrin inclusion complexes led to dose-dependent inhibition of tumor cell proliferation and further reduction of cell viability compared with free carvacrol. In addition, carvacrol/β-cyclodextrin inclusion complexes significantly reduced cell migration. Thus, carvacrol in β-cyclodextrin demonstrated a potential antiproliferative effect, representing a promising alternative in the treatment of prostate cancer. **Acknowledgments:** CAPES, CNPq, FINEP and FAPITEC/SE for the financial support and fellowships.

**Indoleamine 2 3-dioxygenase (IDO) enzyme can contributes to the resistance of human melanoma naïve and resistant to BRAF inhibitor**

**Introduction:** Melanoma is one of the most immunogenic tumors and its relationship with immune system is currently under investigation. IDO, an enzyme expressed by immune and tumor cells as melanoma, is considered one of molecules involved in immune escape and tumor progression. Therefore, it is possible that IDO has a role in such resistance. Thus, our aim is to evaluate IDO presence during melanoma progression and the impact of BRAFi over IDO in naïve and resistant melanoma cell lines. **Methods:** Patient melanoma tissue samples – nevi (3), primary melanoma (3) and melanoma metastasis (2) were evaluated through immunohistochemistry (IHC) for IDO expression. IFN-γ-induced IDO expression was verified under the absence/presence of vemurafenib (BRAFi) in 8 different melanoma cell lines: SK-MEL-28, SK-MEL-29, A375, WM164, naïve (N) and BRAF resistant (R) cell lines. Also, in silico studies for IDO in melanoma progression and resistance was performed through R programming using GEO Gene series repository. **Results/Discussion:** Primary melanoma and metastasis samples presented a stronger IDO immunostaining while in 2 samples of nevius the labeling was weaker. These results are similar to bioinformatics analysis of GSE12391 series. Investigating IDO protein expression, SK-MEL-29/N/R, SK-MEL-28/N, A375/N, BRAFi downregulated IDO expression. On the other hand, WM164/N presented an increase of IDO expression. The resistant lineages of A375, WM164 and SK-MEL-28 did not have IDO expression regulated by BRAFi. **Conclusion:** A downregulation of IDO expression by vemurafenib seems to be a trend among the samples. The IHC and bioinformatics analyses indicate an increase of IDO during disease progression. **Financial support:** Thematic Project FAPESP # 17/04926-6 / Fellowship: CNPq
EXOSOMES FROM PROSTATE CANCER CELL LINE CONFER PRO-ANGIOGENIC CHARACTER TO ENDOTHELIAL CELL LINE

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Introduction Exosomes are small vesicles secreted by cells and are important in the communication between cancer cells and the microenvironment, being able to carry proteins, miRNAs, microRNA, and DNA. The microRNAs are small non-coding RNA molecules that regulate gene expression and are stable in circulating samples due to its incorporation in exosomes. The aim of this study was to evaluate the effect of exosomes derived from prostate cancer cells on endothelial healthy cells. Methods Exosomes of PC-3 and LNCaP cell culture supernatant were isolated through serial centrifugation. The morphology and size of exosomes were evaluated by Transmission Electron Microscopy (TEM). The total RNA of exosomes were extracted, the quality and amount of RNA were evaluated in a Bioanalyzer and 2549 microRNAs were analysed by microarray. We used both TargetScan and TarBase to predict potential target genes. Tube formation and invasion assays were performed with endothelial cells HUV-EC-C exposed to 5 and 10 µg/mL of PC-3 exosomes.

Results and discussion Isolated vesicles showed a cup-shaped morphology and size (85 and 70 nm, LNCaP and PC-3 respectively) characteristic of exosomes. We identified 52 miRNAs down-regulated and 20 miRNAs up-regulated in PC-3 exosomes. Gene ontology analyses predicted these miRNAs regulate specific angiogenesis pathways. Moreover, in vitro PC-3 exosomes support invasiveness and organization of vessel-like structures of HUV-EC-C cells consistent with pro-angiogenic properties. Conclusions Prostate cancer exosomes showed relationship with vascular remodelling and angiogenesis, being an important property for understanding the progression of the disease and the development of new prostate cancer treatments.

Financial support: CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) and CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior)

EVALUATION OF OXIDATIVE STRESS PARAMETERS IN THE THREE TRIMESTERS OF GESTATION

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Introduction: During pregnancy, changes occur in the body, triggering changes in the use of energy substrates and increased oxygen consumption, in response to fetal growth and maternal physiological changes. Thus, this study aims to evaluate the oxidative stress parameters in the three trimesters of gestation. Methods: Blood samples were collected from pregnant women (n=35) in the first (11th-14th week), second (20th-24th week) and third (30th-34th week) gestation period to estimate thiobarbituric acid-reactive substances – TBARS (Lappen et al., 2001), protein thiol groups (Boyne and Ellman modified by Jacques-Silva et al, 2001) and vitamin C (Jacques-Silva et al, 2001). The study was approved by the Ethics Committee (CAAE: 62643616.2.0000.5346). Statistical analysis was by ANOVA or by Kruskal-Wallis test. Data was expressed as mean±standard deviation or as median (interquartile range), where value of p Results and discussion: In the third gestational trimester, TBARS levels in plasma were significantly higher [7.37(12.08-5.00) vs 4.21(6.37-3.15)], while protein thiol groups were significantly lower [100.9(140.4-91.45) vs 123.3(151.2-102.9)] when compared to the first trimester. TBARS levels in erythrocytes increased during pregnancy [22.30±10.39 vs 35.68±14.07 vs 56.55±18.35] and those of vitamin C decreased [16.81±4.21 vs 13.52±3.26 vs 10.37±4.95], suggesting alterations in the parameters of oxidative stress during the three gestational trimesters. Conclusion: With the results obtained, it was possible to observe an increase in oxidative stress through the TBARS levels, besides the reduction of the protein thiol groups and vitamin C, representatives of the antioxidant system, especially in the last trimester of gestation.
INTRODUCTION: Obese individuals show a greater incidence of depression when compared to the general population, even when adjusting for influential variables. Thus, we examined the potential role of IDO in obese patients and whether weight loss due to bariatric surgery could affect IDO activity, inflammation biomarkers, and clinical outcomes of patients undergoing bariatric surgery.

METHODS: Patients who underwent bariatric surgery had clinical data registered and serum samples collected before and after bariatric surgery (6-month post-operative). IDO activity and levels of the cytokine tumor necrosis factor alpha (TNF-α) were evaluated. Healthy individuals (BMI ≤ 25 kg/m²) were also evaluated.

RESULTS AND DISCUSSION: Forty-three obese individuals and twelve lean subjects were enrolled in the study. Over 41% of patients at the pre-operative used psychotropic drugs, and this percentage did not change significantly at the post-operative period. TNF-α levels were above reference range (8.1 pg/ml) in 56% of patients at pre-operative and 53% at post-operative. Tryptophan and kynurenine levels showed a significant decrease 6 months after surgery (40.5 versus 27.4 µM and 2.16 versus 1.40 µM, respectively; p < 0.01) but unaltered IDO activity (59.6 versus 53.8) in obese patients. Lean subjects showed higher levels of tryptophan (49.7 µM; p < 0.001), and lower IDO activity (34.1; p < 0.0001) when compared to obese patients in both periods.

CONCLUSION: Our data suggest that the weight loss that occurs six months after bariatric surgery is insufficient to revert obesity-induced inflammation scenario that maintains the kynurenine pathway active, leading to unaltered outcomes of neuropsychiatric disorders.

SCHISTOSOMICIDAL ACTIVITY EVALUATION AND CHEMICAL CHARACTERIZATION OF ACYROCLINE SATUREIOIDES (LAM.) D.C. BY UPLC-MS QTOF

Schistosomiasis is one of the most prevalent parasitic diseases in the world affecting around 280 million people in 74 countries. It is Caused by a trematodes platyhelminths from the genus Schistosoma and its prevalence is related to inadequacy of basic sanitation and the presence of the host mollusk. Its an endemic disease In Brazil considered as a serious problem of public health, which causes 280,000 deaths annually. Actually, the treatment relies on a single drug, Praziquantel. However, lineages of resistant parasites to praziquantel have been reported. Therefore, the search for new medicines has been increased over the past years, mainly against the new resistant lineages. Medicinal plants have been considered a great source of new potential drugs against parasitosis including schistosomiasis. This work aimed to test an extract of Achyrocline satureioides (Lam.) D.C. against S. mansoni and identify the majority substances present on it. METHODS: Fresh aerial parts were submitted to extraction with dichloromethane:ethanol. The obtained extract was assessed against S. mansoni worms in different concentrations (25, 50, 100 and 200 µg/mL) and different times (24, 48 and 72 hours). The extract was subject to UPLC-MS QTOF analysis in positive and negative mode. RESULTS AND DISCUSSION: The specie presents a significative activity against adult worms, resulting in a decreased motor activities and death in 100% of parasites. Four substances were identified, 3-O-Methylquercetin, 3'-O-Methyluteolin, Apigenin and Dihydromethysticin. Conclusion: A. satureioides demonstrated a great schistosomicidal activity, revealing a possible way to further studies and discovery of novel drugs against Schistosomiasis.
EXO-MICRONAs PROFILE FROM PROSTATE CANCER CELLS AS POTENTIAL BIOMARKERS

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Introduction: The main tool for prostate cancer diagnosis is serum concentration of prostate-specific antigen (PSA). However, 75% of all men with elevated PSA level don’t have cancer. For this reason, it is important the identification of new biomarkers that are capable of distinguishing the cancer. The microRNAs are small non-coding RNA molecules that regulate gene expression and play an important role in tumorigenesis. Moreover, microRNAs are stable in circulating samples due to its incorporation in exosomes. Therefore, the aim of this study was to identify the miRNA expression profile of exosomes derived from prostate cancer cell lines to suggest new biomarkers. Methods: The exosomes of 3 human prostate cell lines (RWPE-1, LNCaP and PC-3) were purified from cell culture supernatant by sequential centrifugation and analyzed by transmission electron microscope. After, total RNA of exosomes and donor cells were extracted, the quality and amount of RNA were evaluated in Bioanalyzer and 2549 microRNAs were analyzed by microarray. Results and discussion: The isolated vesicles showed a cup-shaped morphology and size characteristic of exosomes. Moreover, the RNA electropherograms indicate the majority presence of small RNAs (Financial support: CNPq and CAPES).

ZINC DEFICIENCY IMPAIRS 3T3-L1 ADIPOGENESIS BUT PROMOTES VISCERAL ADIPOSE TISSUE INFLAMMATION AND EXPANSION AFTER A 3-MONTH HIGH CARBOHYDRATE–DIET IN MICE

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Introduction: Zinc deficiency is associated with low-grade inflammation in hypertrophic adipocytes and insulin resistance. Insulin can bind to zinc improving solubility in beta cells and may contribute to insulin binding capacity to its receptor. We aimed to verify the influence of zinc deficiency in adipogenesis and in mice after a short-term carbohydrate overfeeding. Methods: Proliferation and differentiation of 3T3-L1 preadipocytes exposed to zinc-deficient (ZD) or zinc-adequate (ZA) medium were assessed. Mice (CEUA/UFSC PP00892) were fed with high carbohydrate diet (HCD) containing adequate Zn (HCD-ZA) or deficient Zn (HCD-ZD) for three months. Leptin, adiponectin and the pro-inflammatory adipokine serum amyloid A (SAA) were determined and adipose tissue was analyzed. Results and discussion: In ZD-treated preadipocytes, a decrease of 51% of cells in S-phase was observed. ZD cells exhibited a reduced ability to differentiate demonstrating decreased intracellular lipid accumulation. In animals, zinc deficiency promoted differences in weight gain from day 11 through day 90 (2.69%) when compared to HCD-ZA mice (-2.07%, p<0.01 versus 8±0.2 ng/mL) while leptin increased significantly (31±2 versus 25±3 ng/mL). Conclusion: Zn deficiency reduces proliferation of 3T3-L1 and the ability of cells to differentiate. In addition, a 3-month HCD deficient in Zn promoted inflammation and expansion of the adipose tissue.
ANALITICAL QUALITY AT CLINICAL LABORATORY: A SYSTEMATIC APPROACH FOR PERFORMANCE ANALYSIS OF LABORATORY TESTS

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Introduction: Laboratory tests are important for diagnostic, prognostic, and therapeutic monitoring. In this way, clinical laboratories must ensure the quality of their results by identifying the amplitude of analytical errors (random error, bias and total error).

Methods: Monitoring analytical quality of laboratory tests were systematically approached using random error, bias and total error by a spreadsheet (MS Excel) of 53 biochemical parameters and classified as optimal, desired and minimum in comparison to the literature, historical goals and sigma metrics. Results and discussion: Mensal analytical coefficient of variation was optimal or desired for 88% (n= 47), minimum for 8% (n=4) and 4% (n=2) did not achieve the minimum eligible criteria. Bias based on proficiency tests was optimal or desired for 44% (n= 22), minimum for 20% (n=10) and 36% (n=18) did not achieve the minimum eligible criteria. Analytical total error was optimal or desired for 64% (n=32), minimum for 22% (n=11) and 14% (n=7) did not achieve the minimum eligible criteria. These results demonstrate a robust quality process, but also show the lack of systematic errors or inadequate results for parameters that did not achieve the minimum eligible criteria as well as negative sigma results represent parameters that did not achieve the minimum criteria for analytical bias and total error. Conclusions: Systematic quality approach for analytical laboratory tests makes easier the error preventions. In addition, laboratory specialists have been discussing a model based on biological variation, since specifications based on imprecision and bias cannot represent the practical tolerance for laboratory tests.

ANALYSIS OF LBMPL VACCINE IMMUNOTHERAPEUTIC EFFECTS IN Leishmania infantum NATURALLY INFECTED DOGS

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Introduction: Visceral leishmaniasis, caused by Leishmania infantum, is the most fatal form of leishmaniasis. Currently, there is no safety/effective prophylactic strategy and the chemotherapy shows problems like resistance, toxicity and high cost. Therefore, our group aimed to evaluate the immunotherapeutic effect of the vaccine composed by Leishmania braziliensis antigens plus monophosphoryl lipid A in symptomatic dogs naturally infected with L. infantum. Methods: Dogs were submitted to three series of immunotherapy with LBMPL, then 90 following-days it was analyzed, by real-time PCR, the parasite burden in spleen, histopathological alterations and it was made an immunophenotyping by flow cytometry analysis. Results: After immunotherapy with LBMPL dogs, it had an increase of T-CD3+ circulating-lymphocytes synchronous with T-CD4+ and T-CD8+ subsets. Otherwise, a decrease of CD21+B cells was observed. Furthermore, increased NK cells (CD5-CD16+) and CD14+ monocytes were observed in animals after immunotherapy. Analyzing the splenic histopathological alterations, LBMPL group showed a 30% of reduction in hyperemia when compared to MPL and symptomatic groups. Additionally, it was observed a decrease in nodular hyperplasia in the LBMPL animals when compared to the other groups. Both the LBMPL and the MPL groups showed reduction in white pulp depletion and red pulp hyperplasia when compared to symptomatic dogs. Associating with these results, spleen parasite burden showed an intense reduction in the LBMPL dogs when compared to the MPL group. Conclusion: The immunotherapy with LBMPL vaccine was able to reestablish the immune response, reduce spleen alterations with controlling the lesions mainly associated with the parasitism control.

Ethical approval: The study protocol was approved by the Ethical Committee for the Use of Experimental Animals of the Universidade Federal de Ouro Preto, Ouro Preto, MG, Brazil, under the protocol number 2010/57.

Financial support: FAPEMIG, CNPq, UFOP, UFMG.
TISSUE REPAIR OF MICE WITH FISH OIL SUPPLEMENTS

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Essential fatty acids, especially α-linolenic (n-3), are associated with tissue repair and wound healing. Studies claim that n-3 favors the autolytic debridement of the lesion, inducing granulation and accelerating healing. Currently, the population has been looking for forms of supplementation these fatty acids, such as fish oil capsules. This study was submitted to evaluation and approved by the Commission of Ethics in the use of Animals (CEUA) of the Federal University of Rio de Janeiro (Protocol MAC043). On the 21st day of life, 24 mice Swiss (Mus musculus) were anesthetized to perform a tissue lesion. These were randomly divided into 3 groups (n = 8): Control group (GC) - treated with physiological solution; Group Omega Three 1 (GOT1) - treated with synthetic n-3 1; Group Omega 3 2 (GOT2) - treated with synthetic n-3 2. During the experiment (21 days), the animals were kept in individual cages, the wounds were weekly evaluated and photographed and the images were imported into the ImageJ software to measure. The difference between the size of the wounds was analyzed by the ANOVA and T test and the level of significance (p) used was 0.05. Throughout the experiment, it was observed that there was no statistical significance between the groups, although numerically and visually, this difference was clearly observed in the GOT2, which showed a greater cicatrization, suggesting a possible adulteration of the oil used in GOT1, that needs to be substantiated by subsequent physical - chemical studies. Thanks to FAPERJ for granting a scientific initiation scholarship.

CHRONIC LYMPHOCYTIC LEUKEMIA: PROTEIN KINASE AKT AND MICRONAS GENE EXPRESSION EVALUATION AND THEIR IMPORTANCE IN DISEASE PATHOGENESIS

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Introduction: Chronic lymphocytic leukemia (CLL) is recognized by heterogeneous clinical course and cannot be accurately predicted by clinical staging systems. This leads to investigation of prognostic markers that can add predictive value to staging systems. The present study aimed to evaluate markers with potential for diagnosis and prognosis focusing on AKT protein kinase and microRNAs expression in individuals with CLL compared to controls. Methods: We evaluated 60 individuals diagnosed with CLL at the Hematology Service. The same analyzes were performed in 44 individuals, apparently healthy and without previous history of leukemia (control group). The consent term was obtained from all participants according to the privacy law. AKT and microRNAs gene expression was assessed by qPCR, using oligonucleotides previously described. Results and discussion: There was a significant increase in AKT gene expression in patients when compared to controls (p= 0.017). Considering Binet staging groups, a significant difference was observed between the groups, being higher in the B+C group (p= 0.013). The miR-27a, miR-let-7b, miR-21 and miR-26a microRNAs were also evaluated in CLL patients and in the control group. No significant differences were observed in miR-27a and miR-21 gene expression when compared to controls. On the other hand, there was a significant increase in miR-let-7b (p= Conclusion: Increase of AKT protein kinase and miR-let-7b and miR-26a reduction in CLL patients may explain, at least in part, the increase in lymphocytes survival in these patients. Acknowledgments: The authors are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Pro-Reitoria de Pesquisa (PRPq) da Universidade Federal de Minas Gerais, for sponsoring this investigation.
CHARACTERIZATION AND EXPRESSION OF THE TCR/CD3 CHAIN GENES OF THE EXTRACELLULAR VESICLES, BEFORE AND AFTER EXPOSURE TO FLUDARABINE, IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction: Immune disorders in chronic lymphocytic leukemia (CLL) is a clinical problem. This leads to investigation of prognostic markers that can add predictive value to staging systems. Methods: In order to elucidate the feature of extracellular vesicles (EVs) in this CLL disruption, culture of peripheral mononuclear cells from 28 CLL patients and 24 healthy individuals matched by age and sex (control group), were performed to evaluate EVs: size distribution by dynamic light scattering and nanoparticle tracking; interference on gene expression of CD3/TCR complex (γ, δ, ε, and ζ) by qPCR; immunophenotyping by flow cytometry; and protein profile on SDS-PAGE. The institutional Ethics Committee of Federal University of Minas Gerais approved this study (CAAE-021776120.0000.5149), and informed consent was obtained from all participants. This study was carried out in accordance with the Declaration of Helsinki. Results and discussion: The EVs sizes among patients, their clinical classifications and controls showed no significant difference. Significant lower expression levels of CD3 ε and ζ chain genes were found in patients compared to the controls (p = 0.014 and p = 0.008 respectively), and there was a greater carry of these genes by the patient EVs than controls subjects. There was a subtle difference of protein profile in EVs from moderate risk patients (Binet B). Immunophenotyping confirmed predominance of EVs from lymphocytes. The estimated concentration of EVs of controls, the non-exposed and exposed EVs to fludarabine in culture was 9.66e+008 (+/- 0.35e+007); 1.19e+009 (+/- 0.73e+007); and 7.61e+008 (+/- 0.48e+007) particles per ml respectively. Conclusion: the data suggest the potential role of EVs in the CLL on maintenance of pathogenic microenvironment due to their increase in number, interference in the expression of CD3 chain genes and variation in their protein profile.

Acknowledgments: The authors are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Pro-Reitoria de Pesquisa (PRPq) da Universidade Federal de Minas Gerais, for sponsoring this investigation.

METABOLIC PROFILE: CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction: Chronic lymphocytic leukemia (CLL) is one of the most common lymphoid malignancies that result in quantitative and qualitative changes in blood cells (B lymphocytes). Metabolomics is a recent analytical approach that aims to identify and quantify metabolites present in biological samples. In this context, an application of these analyzes in patients with leukemias is still incipient. Methods: Plasma samples from 22 patients with CLL and of 19 healthy individuals who constituted the control group were analyzed. Metabolites were analyzed using a quantitative and controlled metabolomic target based on Absolute / DQ® p180 Kit (Biocrates Life Sciences AG, Innsbruck, Austria) instructions. The Ultra Performance Liquid Chromatography (UPLC) technique associated with the tandem quadrupole mass analyzer was used. Results and discussion: The validated assay allowed a comprehensive identification and quantification of 186 endogenous metabolites, including 21 amino acids, 19 biogenic amines, 40 acylcarnitines, 90 glycerophospholipids, 15 sphingolipids and 1 sum of hexose. The data were based on multivariate statistical methods (SIMCAp + (14.0.1, MKS) and univariate (MATLAB). The PCA, PLS-DA and OPLS-DA statistical models were used to create a metabolic ranking. Metabolic routes were analyzed through HMDB, KEGG and MBROLE databases. It were selected some metabolites that were which were highlighted by an increase (citruline, glutamate, threonine, asparagine) or decrease (glycerophospholipids) in concentration levels in CLL when compared to control group. Conclusion: Metabolic profile preliminary analysis of this experiment allowed identification of metabolites related to cancer metabolism processes, which may be considered possible targets for future research of diagnostic and prognostic markers as well as therapeutic targets.

Acknowledgments: The authors are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Pro-Reitoria de Pesquisa (PRPq) da Universidade Federal de Minas Gerais, for sponsoring this investigation.
OBESITY AND ORAL CONTRACEPTIVES: EVALUATION OF CARDIOMETABOLIC PARAMETERS

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Introduction: Combined oral contraceptive (COC) use has been associated with an unfavourable impact on the carbohydrate and lipid metabolism of both normal-weight and obese women. Methods: We performed a cross-sectional study to verify the cardiovascular parameters as blood pressure, fasting serum glucose, lipid and inflammatory profile in a population of women aged 15-45 years, considering obesity and COCs use. Our casuistic was constituted of 481 women using COCs and 110 women age-matched and COC non-users, classified as obese and nonobese according to the body mass index. The study was approved by the ethics committee of CPqGM-FIOCRUZ (CAAE 08290812.0.0000.0040. Data were collected from August 2013 to July 2014. Results and discussion: COCs use and obesity were associated with increased systolic (P≤0.001) and diastolic blood pressure (P=0.01), total cholesterol (P=0.002), LDL cholesterol (P=0.001), very low density lipoprotein cholesterol (P=0.001), triglycerides (P=0.001), ferritin (P=0.006), C-reactive protein (CRP) (P≤0.001) and Nitric oxide metabolites (P≤0.001) and decreased high density lipoprotein cholesterol (HDL-c) (P≤0.001) level. However, only CRP and HDL-c levels were considered out of normal limits, which are reported as markers associated with cardiovascular risk. The odds of having low level of HDL-c and high level of CRP was increased among obese women in the COCs users group. COCs use was independently associated with low levels of HDL-c, especially 2nd generation progestins (P2nd generation progestins. We observed that obesity and COCs use were associated with alterations in laboratorial parameters related to development of cardiovascular disease, especially in decreasing HDL-c levels and increasing CRP concentrations. Moreover, COC use, especially those with 2nd generation progestins, was associated independently with low levels of HDL-c. Conclusions: No clinical significant association among obese women COCs users and lipid and inflammatory biomarkers were found for the majority of cardiometabolic parameters. However, considering obesity and COCs use, both seem to be associated with low level of HDL-c and high level of CRP, which are associated with cardiovascular risk.

EVALUATION OF EGF AND FGF2 ON MELANOGENESIS AND VIABILITY OF MURINE MELANOMA B16F10 CELLS

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Introduction: Melanoma is a tumor derived from neural crest melanocyte cells. The melanocytes progenitors express Mitf during migration and their proliferation is influenced by Epidermal Growth Factor (EGF), while Fibroblast Growth Factor 2 (FGF2) induces neural crest multipotent progenitor renewal. Considering the results obtained with EGF and FGF2 in neural crest cells, and due to the fact that some melanoma lineages express EGF receptors and FGF2, the aim of this study was to ascertain the influence of these growth factors on melanogenesis and cellular viability on B16F10 lineage. Methods: The lineage B16F10 was immunostained with anti-Mitf. The cells were exposed to EGF (0.01ug/mL; 0.1 ug/mL; 1 ug/mL and 10 ug/mL) and FGF2 (10ng/mL), and their viability was assessed by MTS assay. The melanogenesis was qualitative and quantitative analyzed in comparison with αMSH (10 nM) and IBMX (50 nM). Results and discussion: The lineage B16F10 expresses the transcription factor Mitf. However the growth factors EGF and FGF2 do not present significant influence on cellular viability and melanogenesis of murine melanoma B16F10. Conclusion: The growth factors FGF2 and EGF have not shown the same impact on viability and melanogenesis in melanoma lineage B16F10 as in melanocytes progenitors in embryo development.
DETERMINATION OF PHENOLIC COMPOUNDS BY UHPLC-QQQ-MS/MS ANALYSIS, NUTRITIONAL AND BIOLOGICAL PROPERTIES OF PASSIFLORA LESCHENAULTII FRUITS

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Introduction: Twenty-four phenolic compounds including daidzein, epicatechin, (±)-catechin, cinnamic acid, parcoumaric acid, ethyl gallate, ferulic acid, luteolin, naringenin, quercetin-3-glucoside, vanillin, pinocembrin and artepillin C were identified first time in the fruits of Passiflora leschenaultii by using UHPLC-QqQ-MS/MS analysis. Method: The proximate composition, anti-radical and anti-diabetic activities of different solvent extracts were also determined by the biological assays. Results and discussion: The fresh fruit pulp of P. leschenaultii registered higher total phenolic (691.90 mg GAE/g extract) and tannin (313.81 mg GAE/g extract) contents and it also exhibited very high DPPH• (IC50 of 6.69 µg/ml) and ABTS+• (9760.44 µM trolox equivalent/g extract) scavenging activities. The fresh fruit pulp showed a strong inhibition towards the key enzymes α-amylase and α-glucosidase (IC50 of 32.20 and 19.81 µg/mL, respectively). Conclusion: This work indicates that the phenolic compounds rich fruit pulp of P. leschenaultii can serve as a potential nutraceutical, antioxidative and anti-diabetic agent in food and pharmaceutical formulations.

EFFECT OF CHITOSAN ENCAPSULATED ZINC OXIDE nanoparticleS ON CYTOTOXIC ACTIVITY: A COMPARATIVE STUDY ON BIOLOGICAL (PHOENIX LOUREIROI FRUIT) AND CHEMICAL SYNTHESIS

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Introduction: The synthesis of nanosized materials is recognized to have remarkable potential applications in pharmaceutical drug delivery, especially, green synthesis is an advanced technique for nanomedicine as targeted drug approach with less toxicity. Thus, in the present study, the effect of biocompatibility was studied in the biologically and chemically synthesized Zinc Oxide (ZnO) and chitosan (CTS) encapsulated ZnO (ZnO-CTS) nanoparticles. Methods: Phoenix loureiroi fruit and ammonia were used for the biological and chemical synthesis of ZnO-CTS nanoparticles respectively. The characterization was done by Fourier transform-infrared (FT-IR), X-ray Diffraction (XRD), Scanning Electron Microscopy (SEM), Field Emission-Scanning Transmission Electron Microscopy (FE-STEM), Energy dispersive X-ray spectroscopy (EDX) and Ultra Violet-Diffuse Reflectance Spectroscopy (UV-DRS) analysis. The reactive oxygen species (ROS) level was estimated by the nitrobluetetrazolium assay in vitro. The MTT assay was used to study the effect of nanoparticles on Caco-2 cells. Results: the characterization studies confirmed the chemical structure (H-N-H, O-H, Zn-O), crystalline size (18.60 nm), morphology (spherical), elemental composition (Zn =61.10%; O = 25.86%) and optical properties (λ = 374 nm) of biologically synthesized ZnO-CTS nanoparticles. Biologically synthesized ZnO-CTS nanoparticles enhanced the ROS level (44.50 %) and potentially inhibited the Caco-2 cancerous cell viability (IC50 = 40.46 µg/mL). Conclusion: Biological synthesis is increasingly more important in the pharmacotherapeutic applications in nano herbal drug delivery.
DEVELOPMENT OF A RP-HPLC-MS/MS METHOD FOR SIMULTANEOUS QUANTIFICATION OF SECOND MESSENGERS

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Introduction: Second messengers are used by cells as intracellular signaling, there are different sources of these messengers throughout the body, by a vast array of mechanisms, but usually they consist of cyclic nucleotides and other small molecules, that can be found in low concentrations inside the cell but are readily produced by stimuli. Changes in second messengers concentration are associated with numerous diseases, therefore, the development of a method capable of quantifying those is essential to support the development of new drugs acting in their pathways. Methods: The chromatographic system Agilent 1200 with a Applied Biosystems API 3200 mass spectrometer, in negative mode, was used for the detection of cAMP, cGMP, cCMP, cUMP, cIMP, cTMP, MyoInositol, AMP, GMP. The chromatography method was optimized by testing different chromatographic conditions, such as mobile phase, column, buffers, temperature, and flow rate for separation and mass spectrometry parameters for detection. Results and discussion: Between the tested columns, the XTerra® C18 (2.1 x 150 mm, 3.5 µm) offered the best retention for the targeted compounds. Considering the high sensitivity of the molecules to changes in pH and their high solubility in water, the mobile phase of choice was a gradient elution of water (pH 6) in the first channel and a mixture of acetonitrile:water (95:5) in the second one, both with 2 mM ammonium formate and the flow rate was 400 µL/min. Conclusions: The developed method is suitable for the quantification of the proposed second messengers in preclinical studies on the development of new drugs.

LIGHT TOXICOLOGICAL INVESTIGATION: DEVELOPMENT AND EVALUATION OF AN ALTERNATIVE METHOD

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Introduction: The increasing consumption of light-source technologies reveals that overuse of these devices has increased the incidence of vision problems. In contrast, the use of animals for experiments and tests that evaluate this harm from light to human health has been limited and researchers are looking for new ways to reduce the numbers of animals involved in these studies. Thus, this work aims to develop and evaluate a methodology capable of measuring the damage caused by light using the chorioallantoic membrane (CAM), a model already widely used for the evaluation of drug toxicity and formulations for ocular and cosmetic use. Methods: CAM assay was applied in order to investigate the variation of blood vessels. For this assay, 12 fresh fertilized eggs (Gallus domesticus) per group were exposed to different powers of led (570 nm) and laser (532 nm). Afterward, CAMs were exposed, fixed and analyzed using ImageJ. Angiotool software was used to evaluate changes in the vascular networks, such as vascular density, lacunarity, number of junctions and vessels length. Results and discussion: The excessive exposure recommended by ANSI Z136.1 was able to alter the morphology of the vessels leading to a reduction in the number of junctions and greater lacunarity. However, at lower levels of exposure, could be observed an increase in vessels length that may be related to heat shock proteins. Conclusions: This study presents an alternative to evaluate the toxicity of different wavelengths from different equipment in order to elucidate changes caused by light in the eye. Acknowledgment: CAPES, FAPEMIG, CNPQ.
**A METHOD BY HPLC-MS/MS FOR QUANTIFICATION OF PHOSPHODIESTERASE-5 INHIBITOR**

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**Introduction:** The phosphodiesterase-5 inhibitor is the first line of pharmacological treatment for erectile dysfunction. In order to allow the therapeutic monitoring and pharmacokinetic studies of avanafil, lodenafil, sildenafil, tadalafil, udenafil and vardenafil in plasma, this work aimed to develop a method using High Performance Liquid Chromatography coupled to Mass Spectrometry (HPLC-MS/MS) to quantify these drugs. **Methods:** The parameters were optimized using an HPLC Agilent 1200 coupled to a Triple Quadrupole API 3200 Applied Biosystem® mass spectrometer, provided with electrospray ionization source. Different spectrometric and chromatographic conditions were tested. **Results and discussion:** Through the infusion of the analytes, were established 0.1% formic acid and 3mM ammonium formate as additives and the positive ionization mode. The optimized ion-source parameters were curtain gas: 10 psi; collision gas: 8 psi; capillary voltage: 5500 V; nebulizer and turbo gas: 40 psi; and temperature: 600°C. The ion transition of each compound was: avanafil (m/z 484±375,155), lodenafil (m/z 505.5±487,283), sildenafil (m/z 475±283,100), tadalafil (m/z 390±268,169), udenafil (m/z 517±299,283), vardenafil (m/z 489±312,151) and sulfaquinoxaline (internal standard) (m/z 301±156,108). Chromatographic separation was obtained using a c18column (100x2,1 mm, 5 µm) at 40°C. The mobile phase consisted of (A) water and (B) acetonitrile:water (95:5,v:v), both containing the additives, in the gradient elution mode. The flow rate and injection volume were 200µL.min⁻¹ and 20µL, respectively. The developed method resulted in a chromatogram with well-defined peaks and a good separation of the analytes. **Conclusion:** The method proved to be promising and after validation can be applied in pharmacokinetic and therapeutic monitoring studies.

**METABOLOMICS APPROACH IN MYELODYSPLASTIC SYNDROMES**

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**Introduction:** Myelodysplastic syndromes (MDS) represent a heterogeneous group of hematological diseases with a wide range of clinical and pathological manifestations, which have in common a clonal defect in stem cells. Metabolomics is a recent analytical approach that aims to identify and quantify metabolites present in biological samples. In this context, an application of these analyzes in patients with leukemias is still incipient. **Methods:** Plasma samples from 11 patients with MDS from Hematology/Oncology Service of the Hospital das Clínicas of Universidade Federal de Minas Gerais, and 19 healthy individuals who constituted the control group were analyzed. Metabolites were analyzed using UPLC/Mass analyzer with a quantitative and controlled metabolomic target based on Absolute / DQ® p180 Kit (Biocrates Life Sciences AG, Innsbruck, Austria) instructions. The institutional Ethics Committee of Federal University of Minas Gerais approved this study (CAAE-021776120.0000.5149), and informed consent was obtained from all participants. **Results and discussion:** The statistical models of PCA, PLSDA and OPLSDA generated a list of 143 metabolites. In the multiple univariate analysis (p ≤ 0.05), 140 metabolites were selected. The most representative class was 56% glycerophospholipids; 18% acylcarnitines, 11% amino acids, 10% sphingolipids and 5% biogenic amines. Twenty three of these metabolites had an association in the pathways: choline metabolism and central carbon metabolism in cancer. Metabolites that appear to be linked to the choline metabolism pathway in cancer are related to genetic changes associated with oncogenes: RAS, PI3K, AKT, C-Myc and tumor suppressor genes: SIRT3, SIRT6, p53. **Conclusion:** Preliminary metabolic profile analysis of this experiment allowed identification of metabolites related to cancer metabolism processes, which may be considered possible targets for future research of diagnostic and prognostic markers as well as therapeutic targets. **Acknowledgments:** The authors are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Pro-Reitoria de Pesquisa (PRPq) da Universidade Federal de Minas Gerais, for sponsoring this investigation.
INVESTIGATION OF PLASMA BIOMARKERS WITH UPLC-ESI-QTF-MS ASSOCIATED WITH CHEMOMETRICS OF HOUSEHOLD CONTACTS LEPROSY

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Introduction: Leprosy still represents a health problem in Brazil and in the world. This disease, caused by Mycobacterium leprae, affects the skin and the peripheral nervous system. Actually clinical symptoms are used for diagnosis being unspecific for a rapid and reliable diagnosis. In this study, plasma was used of people living with patients diagnosed with leprosy and compared to a control group. Methods: Plasmas were used from individuals who lived with people diagnosed with leprosy and compared with healthy individuals. The blood was collected in a tube containing ethylenediamine tetraacetic acid (EDTA) and pre-treated the samples for the precipitation of high molecular weight proteins. After the injection of the samples in the UPLC-ESI-qTOF-MS, the acquired data were analyzed by means of chemometric analyzes. The chromatography parameters and the mass spectrometer were optimized. Results and discussion: Experimental m/z ratios obtained by high-resolution ESI-qTOF-MS were compared to their theoretical equivalent, taken from LIPID MAPS and HMDB. The maximum error was set at 2 ppm. With the use of chemometrics, it was possible to separate the group of contacts from the healthy volunteers. Of the masses that were responsible for the 19 m/z separation were super expressed in the contactors when compared to healthy volunteers. Conclusions: The studies of the 19 m/z responsible for discrimination between the groups are in the phase of identifying the metabolic pathways that regulate and can be used as possible early biomarkers of leprosy.

Ethical approval: The project was approved by the Research Ethics Committee with CAAE 56177616.0.0000.0102
Development agency: National Council for scientific and technological development (CNPq).

GENOTOXICITY OF FORMALDEHYDE IN BEAUTY SALON WORKERS OF METROPOLITAN REGION OF PORTO ALEGRE CITY

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Introduction: Formaldehyde (FD) is a widely used aldehyde, which is considered carcinogenic to humans. Studies indicate that FD exposures could induce genotoxic damage. Thus, the aim of this study was to investigate genotoxic effects in salon workers exposed to FD. Methods: The exposure to FD was monitored by UMEx-100 passive samplers fixed near the breathing zone of the individuals and the comet assay was assessed using plasma samples. The sample comprised two groups: 38 workers occupationally exposed to FD in beauty salons and 42 controls. Results and Discussion: The median FD exposure for the exposed and control group were 0.041 ppm (0.020-0.098) vs 0.01 ppm (0.008-0.023) with significant statistical difference (p<0.05) and in tail length (TL: 5.17±1.02 vs 4.58±1.00). DNA damage, as %TDNA was correlated with FD in passive samplers (r=0.246, p=0.032).
Conclusion: Our results suggest that FD may increase DNA damage even in low exposures and that comet assay parameters of tail length and percent of DNA in tail may be useful markers of genotoxic effect of FD in humans.
Ethical Approval: The study was carried out under approval of the Research Ethics Committee of Feevale University (CAAE 59967716.2.0000.5348).
Financial Support: FAPERGS/PPSUS, CAPES.
Section
Drug discovery, medicinal chemistry and molecular medicine
ANTIFUNGAL ACTIVITY OF QUINOLINE DERIVATIVES AGAINST CRYPTOCOCCUS NEOFORMANS

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Introduction: Cryptococcosis is a fungal infection caused by an opportunistic yeast of the genus Cryptococcus. Although the treatment of this infection by amphotericin B, 5-fluorocytosine and fluconazole is frequently effective, there have been a number of reports on cryptococcal resistance. This fact drives the search for treatment alternatives. An important class of compounds for new drug development are the quinoline derivatives, which have been tested with diverse pharmacological activity.

Methods: The minimal inhibitory concentration (MIC) from 22 quinoline derivatives against Cryptococcus neoformans (H99 strain) was performed by broth microdilution assay. From the results, the molecules that presented the best antifungal activity (MIC≤32µg/ml) were selected and the citotoxity was evaluated by red blood cells lysis (RBC) assay.

Results and discussion: The susceptibility assay showed that the molecules IO_AB7, IO_AB11, IO_AB15, IO_AB21, IO_AB23, IO_AB25 and IO_AB30 were able to inhibit C. neoformans with MICs of 1-64µg/ml. Among the tested molecules, IO_AB7 and IO_AB11 were the most effective, presenting MIC of 1–4µg/ml and fungicidal activity at the concentration of 8-16 µg/ml. None of these molecules caused haemolysis on RBC, even in the higher concentration tested (128 µg/ml).

The obtained results corroborate with the literature, which reports that quinoline derivatives possess varied biological activities, including antimicrobial activity.

Conclusion: Our preliminary results indicated that quinolones derivatives promote growth inhibition of C. neoformans and do not present cytotoxic effect. These data highlight the potential of these molecules as antifungal agents to treat cryptococcosis, but more experiments should be performed to prove the anti-cryptococcal efficacy.


SYNTHESIS AND EVALUATION OF ANTIFUNGAL ACTIVITY OF HETEROCYCLIC COMPOUNDS

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Introduction: In recent years, the incidence of fungal infections has increased significantly, and despite current therapy, mortality rates are high. Among fungi of clinical interest, the Candida e Cryptococcus species have attracted attention and constitute a serious problem for public health. The development of novel antifungal agents is still mandatory because of the serious side effects of available drugs and emergence of resistance. Previous studies developed by our research group have shown that some thiazolylhydrazine derivatives display potent antifungal activity, similar to amphotericin B and fluconazole. These compounds served as lead structures for the design of new analogues.

Objectives: The aim of this work is to synthesize and evaluate the antifungal activity of a series of heterocycle-based compounds.

Methods: 1,2,3-triazole derivatives were obtained from “click” reactions. 5-substituted-1H-tetrazoles were prepared from a reaction between p-substituted benzotriazoles and sodium azide, followed by alkylation with different alkyl halides. 1,3,4-oxadiazole derivatives were prepared from the corresponding tetrazole and acetic anhydride. All compounds were characterized by melting point determination, FT-IR, ¹H and ¹³C NMR spectroscopy. The heterocyclic compounds synthesized were evaluated in vitro against Candida and Cryptococcus species.

Results and discussion: A series of heterocyclic derivatives was successfully synthesized. However, the obtained compounds were inactive at 250 mM against seven clinically important fungal species, indicating that the presence of the thiazolyl hydrazine scaffold is essential for the activity.

Conclusions: The results obtained in this work will be used to establish a structure-activity relationship for designing of new analogues with improved activity and pharmacophore searches.

Financial support: FAPEMIG, CNPq
Introduction: Parkinson’s disease (PD) is a progressive neurodegenerative disorder characterized by clinical signs related to motor disorders. PD is associated with the absence of dopamine in striatum, degeneration of dopaminergic neurons, and the formation of Lewy bodies, mainly comprised of α-synuclein protein. Little is known about the mechanism which contributes to the α-synuclein aggregation. Compounds such as apocynin (AP) and diacopcin (DI) present potential antiparkinsonian activity and it are objects of study in new drugs design. In this work AP and DI were submitted to evaluation of inhibition of PD symptoms using in vivo paraquat-induced neurotoxicity in Drosophila melanogaster (DM), and in silico molecular docking against the target NADPH oxidase 1 (NOX-1) in which mediates α-synucleinopathy in Parkinson’s disease. Method: The inhibition of PD symptoms using in vivo paraquat (PQ) induced neurotoxicity in DM were performed to AP and DI in concentration of 0.1 μM, according the continuous liquid feeding method to determine the survival rates and locomotor activity. The molecular modeling evolved the design of chemical structures of AP and DI using Spartan 08 software, and the geometric optimizations and conformational analysis (variation of 30° angles) calculations using the DFT/B3LYP/6.31G*. The lower energy conformers and 3D structure of the enzyme NOX-1 (PDB: 1K4U) were submitted to molecular docking analysis using Igemdock 2.1 software. Results and discussion: The exposure of DM to PQ (0.1 μM) reproduced basic aspects of PD. Neurprotective effect of AP and DI (0.1 μM) showed similar profile to each other in experimental conditions of days 1-4, and the survival rates in day 4 was 35.5% higher than the control of paraquat. In molecular docking studies, the energy values of main interactions between the molecules and the NOX-1 were -87.47 and -65.11 Kcal mol⁻¹ to DI and AP, respectively. In this model, AP presented molecular interactions with the key amino acid residues VAL-365 and ARG-368 closest to amino acids SER-348 and SER-370 compared to DI. This data suggests that AP may exhibit better interaction with NOX-1 in comparison with DI. Conclusion: AP and DI showed reduction of effects caused by PQ, which are similar to PD symptoms. AP presents better interactions with the NOX-1 active site in computational model. These data suggest that both compounds are potential molecules to be used in study and design of novel antiparkinsonian drugs.

SELECTIVE PHOTODYNAMIC EFFECTS ON CERVICAL CANCER CELLS PROVIDED BY P123 PLURONIC MODULATING HYPERICIN DELIVERY

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Photodynamic therapy (PDT) is a minimally invasive treatment modality to use in cervical cancer (CC). Hypericin is a promising agent on PDT, however is highly hydrophobic and the encapsulation with pluronic P123 can overcome this problem. Here, we report the tumor-selective cell internalization, phototoxicity, antimitratory and reactive oxygen species (ROS) generation by HYP/P123-PDT in cervical cancer cell lines (CCCL) HeLa, SiHa, CaSki and C33A compared to a non-tumorigenic cell line, HaCaT. Delivery of HYP/P123 was confirmed by fluorescence microscopy. The citotoxicity of HYP/P123 was assessed by MTT assay in the presence and absence of light. Long-term cytotoxicity was performed by clonogenic assay. Cell migration was determined by the wound-healing assay. ROS generation was measured using spectrophotometric assay. HYP/P123 delivery in CCCL was detected through the emitted red fluorescence inside the cells visualized in fluorescence microscopy with higher intensity in CCCL compared to HaCaT. Phototoxicity was evident in CCCL but not in HaCaT, with reduction of viable CCCL in the lowest concentration of HYP/P123. In the absence of light, there was no decrease in cell viability in all cell lines. The clonogenic potential was reduced in dose-time-dependent manner in 7 and 14 days. The wound-healing assay revealed that HYP/P123 effectively...
inhibited cell migration. Total ROS production significantly increased in CCLS but not in HaCaT, proving that ROS production is the main mechanism of action in PDT. PDT with low doses of HYP/P123 presented selective effect in CCCL and no damage in HaCaT, suggesting a promising agent for the treatment of CC.

Financial support: This work was supported by grants from Brazilian Government (PROCAD 88881.068413/2014-01).

PHOTODYNAMIC ACTIVITY OF CATIONIC PORFYRINES AGAINST Mycobacterium massiliense

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Non-tuberculous mycobacteria (NTM) are classified as opportunistic pathogens causing local or generalized infections associated with post-surgical infection, especially in hospital environments. In this context, the use of Photodynamic Therapy (PDT) appears as an alternative to combat cell proliferation, including that of highly pathogenic microorganisms. PDT by the application of an activated photosensitizer (PS) is capable of producing reactive oxygen species (ROS) that are especially singlet oxygen, capable of causing photo-oxidation of membranes and microorganisms. Thus, it is believed that the development of bacterial resistance to PS compounds is unlikely because they act nonspecifically on organic materials. The minimum inhibitory concentration (MIC) of PS (meso-tetra [4-N-methylpyridinium] porphyrin; TMePyP) was evaluated by the broth microdilution method according to CLSI, against Mycobacterium massiliense (ATCC 48898) at times of 15, 45 and 90 minutes under irradiation with 40 W visible light. In the absence of light, the MIC was 50 \(\mu\)M and in the presence of light the concentration dropped exponentially, varying according to the irradiation time. Under 15 minutes of exposure the MIC was 1.5625 \(\mu\)M, with 45 minutes this concentration drops to half and finally with 90 minutes it decreases four times the MIC of the shortest exposure time. Therefore, the use of cationic porphyrin TMePyP was a potent photosensitizer against this type of microorganism, since it was able to inhibition of mycobacterial growth even with a short period of illumination and in low concentrations. This result stimulate the deepening in methodologies to new antibacterial strategy against infections caused by NTM.

A NEW PPAR AGONIST (GQ-11) MODULATES IMPAIRED INFLAMMATION AND INDUCES RE-EPITHELIZATION IN DIABETIC WOUND HEALING

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Introduction: Chronic wounds associated with diabetes is an important public health problem, suggesting an emerging search for treatments to prevent healing impairment and decrease amputations incidence. Monocytes/Macrophages play a key role in sustained/impaired inflammation on diabetic wounds and an approach on local administration of PPAR\(\gamma\) agonists may show promising improvements in diabetic wound healing. The aim of this study was to investigate the effects of GQ-11, a partial/dual PPAR\(\alpha/\gamma\) agonist, in diabetic wound healing. Methods: C57BL/6J (db/+1) and BKS.Cg-Dock7\(^m\) +/+ Lepr\(^mib\)/J (db/db) mice were maintained at COMRB/UIC (approved by ACC 15-180) and submitted to surgically induced-wounds at scapula region. After surgery, wounds were treated with vehicle, pioglitazone or GQ-11, for 7 and 10 days. Wounds were sectioned and stained with HE, Trichrome and Mac-3. In addition, bone marrow-derived macrophages (BMDM) from C57BL/6J mice were treated with Vehicle, Pioglitazone or GQ-11, following challenge with LPS or IL-4. Cytokine expression was evaluated by qRT-PCR either for mice wounds or BMDM. Results/Discussion: GQ-11 treatment not only downregulated gene expression of Tnf-\(\alpha\) and Il-\(\beta\) but also upregulated expression of Il-10, Tgf-\(\beta\) and Arg-1 genes both in BMDM and db/db mice. Wounds treated with GQ-11 in db/db mice also showed decreased size after 10 days and re-epithelization increase, as well as, higher collagen content and less Mac-3 staining compared to vehicle. Conclusion: GQ-11 modulated impaired inflammation in db/db mice, regulating expression of pro- and anti-inflammatory cytokines, decreasing macrophage accumulation in wound sites, leading to increased re-epithelization and collagen deposition.

Navigating the Chemical Space of Macrolides

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Several articles have already questioned application of the Lipinski’s rule of five, especially after the publication of the new oral bioavailability parameters described by Veber and Lovering. Macrolides make up one of the most important class of antibiotics, and as a macrocycle, has already been excluded from Lipinski and Verber’s rule. Thus, the aim of this study was to characterize the chemical and physico-chemical space of these drugs in order to identify the physicochemical requirements for the oral bioavailability of this class. First, we obtained the structures of all macrolides, which corresponded to 229 compounds filtered from 2160 molecules from the Integrity (Thomson Reuters) database, in .sdf file format and the physicochemical properties were calculated using the Osiris Data Warrior software. The analyzed descriptors were: Molecular weight (MW), cLogP, H-acceptors, H-donors, Topological polar surface area (TPSA) and Number of rotatable bonds (NRB). As a result, we demonstrated through the calculation of the 90th percentile that macrolides in clinical use present physical chemical parameters beyond the established rules, as: MW - 1120.548; LogP - 8.33654; H-acceptors - 19; H-donors - 8.2; TPSA - 280.896 and NRB - 17.2. As a conclusion, the evaluation of the structural and physicochemical properties of macrolides demonstrated that the criteria applied for drugability of small molecule cannot be applied towards antibiotics drug development. While physical models of permeability for small molecules are well established, the descriptors for bigger molecules are not completely understood, hindering the rational design of cell-permeable, “beyond-Rule-of-5” (bRo5) molecules as therapeutic agents.

Searching for Potential Leishmania amazonensis OPB and OPB2 Inhibitors: ADMET Parameters and Molecular Docking Studies

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Introduction: Therapy of Leishmaniasis has toxic effects, high cost and parasites resistance. Therefore, the search for new drugs is urgent. Oligopeptidases OPB and OPB2 from Leishmania amazonensis were identified as potential targets (1,2). Previous studies have identified molecules from ZINC database as possible dual inhibitors (3). In this context, this work aims to search new analogues of compound 2 (ZINC code 19735155) as potential inhibition of OPBs by in silico ADMET and Molecular Docking studies. Methods: In silico ADMET studies of compound 2 analogues were performed using the program ADMET Predictor™. Molecules with good ADMET profiles were submitted to molecular docking calculations at AutoDock4.2, using parameters described in Sodero, 2016 (3). Results and discussions: In silico ADMET studies were performed with twelve compounds (2a-l). Six molecules presented low toxicity and ADME risks, as well as compound 2. The best ADMET profile were found to compound 2e. Absorption problems were indicated in five molecules (2c, 2g, 2i, 2j, and 2k). Only compound 2k also presented metabolism problems. According to molecular docking results, compound 2e showed better score to OPB and OPB2 than compound 2. Compound 2e also showed interactions with the catalytic triad and binding site residues. Conclusions: This study provides important pharmacokinetic and toxicological information for the development of new leishmanicidal drugs, which may provide better efficacy, reduced treatment time, less cost and less adverse effects over existing therapies. Analogue 2e was selected to further in vitro studies of OPB and OPB2 inhibition and genotoxicity. Acknowledgements: Thanks are due to the FAPERJ, CAPES and CNPQ for funding this work.

References:
ORAL ABSORPTION OF PEPTIDE ANTIBIOTICS BEYOND LIPINKI'S RULE

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Among the reasons that justify the low rate in the innovation of antibiotics is the adoption of new platforms for drug discovery, developed since the 1990’s. The restricted use of the “Lipinski Rule” by pharmaceutical industries also contributed for the limitation on the development of antibiotics, since it excludes molecules capable of breaching prokaryote membranes. Thus, the search for new antibiotics in peptide structures is shown as an alternative for this lack of perspective in the development of new antibiotics. In this work, we analyzed all peptide antibiotics and clinical candidates and performed an extensive analysis on their physicochemical and structural properties, and correlated these with their administration route. Thus, we searched on ChemBl and Integrity databases and selected all peptides drugs in clinical use as antibiotics. In sequence, we calculated the physical chemical parameters (MW, LogP, HDB, HBA, TPSA and NRB) using the software Osiris Data Warrior. Also, we classified the compounds as “oral” or “non-oral” based on the administration route available on the Micromedex Solutions database. As a result, we found that 34% of the peptide antibiotics present oral administration, and, besides, all of these compounds violates at least two parameters stablished by the Lipinski or Veber in previous works. Thus, this study furnishes information that could support peptide drug design, with a new cutoff of known descriptors that go beyond the Rule of Five.

CHEMOMETRIC ANALYSIS OF THE ANTITRYPANOSOMA ACTIVITY OF LINS03 COMPOUNDS

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Introduction: Chagas’ disease, caused by T. cruzi, has two options for treatment, benznidazole and nifurtimox. Both lack efficiency in the chronic phase and are relatively toxic. LINS03 series was designed based on the structure of natural alkylphenols gibbilimbols A and B, active against the trypomastigote form. An initial set had 6 different functional groups in the alkyl chain maintaining the phenol ring. This led to increased antiparasitic activity and cytotoxicity, possibly associated to the phenol. Then, 4 different substitution patterns on the aromatic ring were tested. Activity against the infective form ranged from 4.2-47.7 µM and from 1.33-50.0 µM against the replicative form. A chemometric analysis was carried out to understand the SAR. Methods: Relevant descriptors were calculated in Molinspiration and Marvin 16.1.8.0 softwares. Principal component analysis (PCA) and hierarchical cluster analysis (HCA) was performed using the PAST software. Results and discussion: PC1 and PC2 described ~77% of the variance. PC1 is associated to lipophilic/ionization characteristics whereas PC2 is associated to molecular size and hydrogen-bonding descriptors. The graph showed a separation between active (IC50 < 20 µM against amastigotes) and inactive analogues driven by PC1, PC2 separates the actives into amines and carboxylic derivatives. HCA showed similar clustering, with active analogues grouped and separated according to ionization and lipophilicity. Conclusions: This analysis indicated that there is an ideal range of hydrosolubility and molecular size associated with HBA leading to better activities. Financial support: CNPq (455411/2014-0) and FAPESP (2016/25028-3) for the financial support and fellowship to MTV (FAPESP 2016/00195-4).
COMPARATIVE PHARMACOKINETIC OF EFAVIRENZ PLUS TENOFOVIR AND LAMIVUDINE WITH AND WITHOUT LAYERED DOUBLE HYDROXIDE AS A DRUG DELIVERY SYSTEM

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Introduction: One of the initial HIV/AIDS management for treatment-naive patients involves administration of efavirenz (EFV) plus tenofovir (TNF) and lamivudine (3TC). EFV is classified as class II on the Biopharmaceutics Classification System (BCS) and presents a variable interindividual profile of bioavailability in humans due to the influence of factors such as aqueous solubility and dissolution rate. This erratic bioavailability contributes to the variability of response to disease treatment, which highlights the importance of developing formulations that makes the absorption process less susceptible to interindividual characteristics. The layered double hydroxides (LDH) associated with EFV has been developed as a promising alternative in the development of drug delivery systems.

Methods: Pharmacokinetic evaluation of EFV plus TNF/3TC with and without LDH was made in healthy male rabbits (n=7) by oral administration in a single dose of 50 mg, 25mg and 25 mg, respectively, in capsule. Blood samples (0.5 mL) were collected at predetermined time intervals and the plasma concentrations of EFV were determined by Ultra High-Performance Liquid Chromatography (UHPLC). The pharmacokinetic parameters were calculated through the plasma concentration versus time and compared using the Mann-Whitney Test.

Results and discussion: The pharmacokinetic analysis was performed by one-compartment model. The pharmacokinetic parameters were calculated, and no significant difference was found when EFV plus TNF/3TC administered with or without LDH.

Conclusions: This result demonstrates that LDH system was not effective to improve the absorption of EFV and new efforts must be made to resolve this problem.

Financial Support: FAPESP (nº2011/11239-9 and nº 2015/23843-9); CNPQ (134347/2016-1)

DESIGN AND SYNTHESIS OF POTENTIAL CRUZAIN INHIBITORS BASED ON THE STRUCTURE OF MB12

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Introduction: Cruzain is an essential cysteine protease of Trypanosoma cruzi, the etiologic agent of Chagas disease. MB12 stands out as a non-covalent non-peptidic inhibitor recently discovered. In this context, bioinformatics could help in the prioritization of new MB12 analogs for synthesis. Methods: Retrosynthetic analysis of an MB12 analog afforded an aniline and an amine as starting reagents. Sigma-Aldrich catalog was retrieved and filtered, removing reagents with undesired properties and those considered overpriced. Reaction products were drawn using Reaktor and prepared in Ligprep. The virtual library was filtered, excluding those potentially toxic or highly reactive. Docking with cruzain (PDB 3KKU) was performed on Glide, using HTVS, SP and XP protocols. Final selection considered visual inspection, docking ranking, synthesis viability and rationale of starting materials. Results and discussion: After filtering, 161,288 structures were submitted to HTVS docking and the top 10% poses followed the SP protocol. After inspection of key interactions with the protein, synthesis viability and price sum of the reagents, less than 2000 structures made to the final selection, consisting of a visual inspection of docking poses and reagent acquisition rationale, prioritizing common substructures and those better suited for a SAR construction. It’s important to note that one of the selected compounds resembles the ligand from PDB 3KKU, even though this fact was not considered during compound selection. Conclusions: From thousands of possibilities, we could narrow down the synthesis to a few dozen potential cruzain inhibitors. Bioinformatics provide valuable tools to drug development, helping to minimize resources and effort.

Financial support CAPES, CNPq, FAPEMIG and L’Oréal-UNESCO-ABC “Para Mulheres na Ciência”.

SYNTHESIS AND ANTIMALARIAL ACTIVITY OF NEW FLUOROAMODIAQUINE ANALOGUES

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Malaria is responsible for approximately half a million deaths per year in the world. Based on new cases of resistance of Plasmodium falciparum to antimalarial drugs, the need for research of new antimalarial drug candidates is urgent.1 Molecular docking studies on a series of fluoroamodiaquine (FAQ) analogues were previously conducted by our research group and a synthetic route was planned to obtain new derivatives.2 Here, we propose the synthesis of new FAQ analogues using the previously described methodology.2 The compounds were tested in vitro against a chloroquine resistant strain of Plasmodium falciparum (W2).3,4 The 4-amino-2-(hydroxymethyl)phenol (2) was obtained from the reduction of the 2-fluoro-5-nitrobenzyl alcohol (1). Then, 4-amino-2-(hydroxymethyl)phenol (2) was treated in refluxing ethanol with quinoline 3 to afford alcohol 4 (90%). This intermediate was refluxed in concentrated HCl, yielding desired intermediate 5 in high yield (99%). The FAQ analogues 6a-d, bearing a piperazinyl moiety, were obtained from 5, that was treated with an excess of the appropriate piperazine to afford the expected target compounds (substituents: 1-butylpiperazine, 1-(benzo[d][1,3]dioxol-5-yl)methyl)piperazine, 1-(2-chlorophenyl)piperazine and piperazin-1-yl(tetrahydrofuran-2-yl)methanone), obtaining the analogues of fluoramodiaquine 6a (73%), 6b (38%), 6c (73%) and 6d (37%). All compounds were active in preliminary tests for determination of antimalarial profile. Derivative 6c presented 1.348(±0.28) μM as IC50, while other compounds showed IC50 values lower than 1 μM. Tests in lower concentrations are in progress. These results are good indicators to pursue in vitro and in vivo studies, aiming the search for new efficient and safe therapeutic alternatives for the treatment of malaria.

Acknowledgements: CAPES, CNPq; FAPERJ and FUJB.

References:

PHYSICOCHEMICAL INVESTIGATION AND BIOLOGICAL EVALUATION OF INCLUSION COMPLEXES BETWEEN α-BISABOLOL AND β-CYCLODEXTRIN

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Introduction: α-bisabolol is a naturally occurring volatile terpenoid in plants that possesses strong antileishmanial activity. In this research, α-bisabolol was included into β-cyclodextrin (β-CD), its physicochemical characterization and antileishmanial activity was investigated. Methods: Solid inclusion complexes were prepared by physical mixture (PM), slurry complexation (SC) and freeze-drying (FD) methods. Physicochemical characterization of complexes was carried out using X-Ray diffraction (XRD), nuclear magnetic resonance (NMR), molecular docking and entrapment efficiency (EE%). Finally, the study evaluated in vitro antileishmania effects of free α-bisabolol and its inclusion complexes against promastigote and amastigote forms of Leishmania amazonensis.

Results and discussion: HPLC analyses demonstrated that higher EE was obtained for FD method (75.4%). ROESY spectrum of FD showed appreciable correlation of H-1, H-4 and H-3 protons of α-bisabolol with H’-3, H’-5 and H6’ protons of β-CD. XRD results showed decrease of the crystallinity in the FD complex. In vitro studies of free α-bisabolol indicated an IC50 of 3.8 ± 0.8 μg/ml against the promastigote form and 4.7 ± 1.2 μg/ml against the axenic amastigote form of Leishmania amazonensis. FD complex showed significant activity against promastigote forms (6.3 ± 1.3 μg/ml) compared to PM and SC methods. Cytotoxicity in J774A1 macrophages analysis to free α-bisabolol exhibited a CC50 of 65.7 ± 9.0 μg/ml, which is more cytotoxic than the FD complex values (CC50 = 91.2 ± 7.8 μg/ml). Conclusions: Our present study suggested that the inclusion of α-bisabolol in β-CD cavity improved its physicochemical properties and might be used as an alternative for the treatment of leishmaniasis.

Acknowledgments: CAPES, CNPq, FINEP and FAPITEC/SE for the financial support and fellowships.
Cervical cancer (CC) remains an important cause of cancer related-deaths in woman worldwide. The current treatment presents failure and serious side effects. Chrysin is a natural flavonoid and has been demonstrating promising anticancer properties. This study aimed to evaluate the antitumoral effects of chrysin in a wide panel of CC cell lines (C33A, HeLa, SiHa, CaSki) compared to a nontumorigenic cell line (HaCaT). Cytotoxicity was assessed by MTT assay (concentration of 1.563 to 100μM), morphological changes were observed by microscopy (1.563, 50 and 100μM) and for the following experiments, the treatment was based on inhibitory concentration (IC_{50} and IC_{30}) of each cell. Long-term cytotoxicity was evaluated by clonogenic assay (IC_{30}), cell death pathway by Annexin V-FITC/PI (IC_{30}). Total reactive oxygen species (ROS), mitochondrial transmembrane potential (ΔΨm) and lipid peroxidation (LPO) were determine using spectrofluorometric assays (IC_{50}). The CC migration and invasion potential were evaluated by wound-healing and transwell assays (IC_{30} and IC_{50} respectively). For all the experiments, untreated cells were used as control. The results showed that chrysin had a cytotoxic effect in all cell lines, with higher action on CC cells. The CC cells clonogenic potential was reduced after 7 and 14 days of treatment and chrysin increased changes in cell morphology in CC cells but not in HaCaT. Chrysin acts predominantly via apoptosis and has the capacity to induce selective oxidative damage once ROS production and LPO increased, while ΔΨm decreased in CC cells. Also, chrysin was able to reduce cell migration and invasion. Therefore, chrysin is a possible candidate for the treatment of CC.

Financial Support: This work was supported by grants from Brazilian Government (PROCAD 88881.068413/2014-01).

SYNTHESIS AND ANTIILEISHMANIAL ACTIVITY OF NOVEL PIPERAZINE THIOUREA DERIVATIVES

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Leishmaniasis is an infectious disease, not contagious, based on the protozoa of the genus Leishmania. It is a public health problem in 98 countries, spread across four continents. The many adverse effects to the recommended drugs and the protozoan resistance demonstrate the need for the development of new therapeutic alternatives. The present work has as objective the synthesis and characterization of 34 thiourea derivates (LT), molecules which have the thioureido nucleus bearing a piperazinyl moiety. Furthermore, this work aims the evaluation of these compounds activity against the promastigote and amastigote forms of *Leishmania amazonensis*, the evaluation of macrophages toxicity and the calculation of the selectivity index. The different LTs were synthesized from the reaction between the phenyl, benzyl, phenylethyl or trimethoxyphenyl isothiocyanates with different piperazines. These reactions were conducted at room temperature with solvent CH₂Cl₂, without further purification. Subsequently, they were characterized by ¹H and ¹³C NMR, IR, MS and Melting Point. Its leishmanicidal activity (IC_{50}) was evaluated by conducting an in vitro assay. The 43 LTs obtained excellent yields (70–99%). Among them, LT162 showed better activity against the promastigote form, presenting IC_{50} values of 2.9±2.1 μM, lower values when compared to Miltefosine (IC_{50} 6.9±2.4 μM) the unique oral drug used for the treatment of leishmaniasis. The evaluation of the toxicity in macrophages was also performed. The assays against the amastigote form and the calculation of the selectivity index are in progress. These results demonstrate that the LTs are promising molecules for the development of new therapies for the treatment of leishmaniasis.

Acknowledgements: CAPES, CNPq; FAPERJ.

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1. DNDi, 2018
Molecular Modeling and Molecular Dynamics Simulations of Molecular Systems Containing Polymers and Antithrombotic N-Acylhydrazone Derivatives

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Platelet aggregation is one of the major precursors of cardiovascular accidents and is one of the main events involved in these thrombotic disorders. Moreover, antiplatelet agents available on the market have severe adverse effects on the health of the patient, especially bleeding and recurrent lesions of the unsatisfactory pharmacokinetics, then the development of drug delivery systems may allow superior therapeutic efficacy to conventional formulations. The nanoparticles can be prepared using different materials, of which the polymers are one of the most applied drug carriers. Thus, the main objective of the present work was to study the molecular systems containing poly(lactic-co-glycolic acid) (PLGA) or polycaprolactone (PCL) and 2C compound, an antithrombotic N-acetylhydrazone derivative, applying molecular dynamics simulations. The three-dimensional molecular structures of 2C compound and both polymers monomers were constructed and optimized using the Spartan’10 program. Following the geometry optimization, the polymers chains were increased and added in an initial amorphous cell. Then, the simulation boxes with dimensions 12x12x12 nm3 were prepared in order to insert polymers molecules containing 60 monomers each and 2C molecules at water medium (Xenoview program). The molecular dynamics were performed. The PLGA molecules showed more affinity to 2C molecules than PCL chains. The PLGA molecules dispersed in the aqueous medium interacting with the 2C molecules, while the PCL molecules remained bound together forming a nanoparticle rapidly without influence on the 2C molecules dissolution in water environment. The molecular dynamics simulations results indicated the PLGA as a more favorable polymer to development of nanoparticles containing 2C compound.

In vitro and in vivo study of the possible anti-inflammatory action mechanisms of N-acylhydrochonic substitute derivatives

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NOS and COX-2 enzymes are key-enzymes in the inflammatory response when stimulated primarily by pro-inflammatory cytokines. Compounds that act by modulating the activity of these enzymes are promising in combating inflammation, for example N-acetylhydrazone derivatives. This work aims to evaluate possible mechanisms of anti-inflammatory action of the N-acetylhydrazone derivative: N'-[(1H-indol-3-ylmethylene) -2-cyanoacetohydrazide (JR19). An in vitro test against cyclooxygenase (COXs) was performed. In the carrageenan-induced peritonitis assay (to investigate the participation of the nitric oxide / guanylate cyclase pathway and the cytokine dosage) and gastric toxicity, adult Swiss mice were used. The protocols were approved by the Ethics Committee on the Use of Animals of the CESED (n° 5905022016). The compound (25Mm) shows a SI of 1.51 for COX2, with a percent inhibition of 100% COX-2. In the gastric toxicity test, JR19 (100 mg.kg-1) did not induce ulcerative lesions. In peritonitis, the compound (100 mg.kg-1) was able to reduce, significantly, the number of leukocytes of the peritoneal exudate by 48.3%, in relation to the control and this effect was reverted in the animals pretreated with L-NAME methylene blue, indicating participation of the NO / guanylate cyclase pathway. Cytokines levels of TNF-α, IFN-γ, IL-6 and IL-17 were also significantly reduced. The concentrations of IL-2 and IL-4 cytokines were not altered. Thus, compound JR19 probably acts by interacting with COXs acting selectively on COX-2, by maintaining NO levels and reducing proinflammatory cytokines and without gastric toxic effects.
SYNTHESIS AND LEISHMANICIDAL ACTIVITY IN VITRO OF NOVEL THIOUREA DERIVATIVES

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Introduction: In the world, Leishmaniasis is responsible for an annual registry of 1.0-1.5 million cases. This is an infectious disease caused by protozoa of the genus Leishmania. Thus, the present study searches for new drug candidates since current therapeutic alternatives are costly and can induce serious side-effects, as well as clinical resistance frequently detected¹. Methods: Thiourea derivatives were synthesized from the reaction between the phenyl, benzyl and phenylethyl isothiocyanates with different aliphatic and aromatic amines. The reactions were conducted at room temperature or under reflux². The structures of thioureas were confirmed by ¹H NMR, ¹³C NMR and HRMS³. The leishmanicidal activity (IC₅₀) of them was evaluated in vitro against the promastigote form of L. amazonensis (resazurin). Results & Discussion: The 15 products were obtained with good yields (70-99%) and did not require any further purification after isolation. Among these, 12 thioureas presented better activity against the promastigote form of L. amazonensis, with IC₅₀ values between 19.9 – 80.43 μM, although the IC₅₀ values found were higher than that of miltefosine (promastigote: IC₅₀ 5.6 ± 1.1 μM). The assays against amastigote form and cytotoxicity in mouse peritoneal macrophages are still under way. Conclusion: Based on these results, synthesized new derivatives were obtained with satisfactory yields and were characterized by different physical methods and showed leishmanicidal activity against the promastigote form of L. Amazonensis. This study aims at the search for efficient and safe therapeutic alternatives and collaborates for the rational R&D of new candidates for the treatment of leishmaniasis.

Acknowledgements: CAPES, CNPq; FAPERJ

SYNTHESIS AND BIOLOGICAL ACTIVITIES IN VITRO OF DIOSMIN DERIVATIVE COMPLEXES

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The coordination of metal ions with flavonoids is a methodology applied to improve its pharmacological properties. To evaluate the role of ions on diosmin (a flavone), new complexes with Fe(II), Cu(II) and Co(II) ions were synthetized and characterized by FT-IR, UV, ¹H NMR, mass spectroscopy techniques and elementary analysis. To evaluate the biological activity of coordination compounds in vitro, the antioxidant, antibacterial and antitumoral activities were analysed by the ABTS, disc diffusion, MIC and MTT methods, respectively. Diosmin loses the sugar molecule becoming diosmetin (D), that coordinated in a ratio of 1D:1Fe and in a ratio of 1D:2Cu or Co. However, in this case, diosmetin loses the methyl group at C4’ and H at C3’ producing a new ligand and complexes. The coordination of Cu and Fe improve the antioxidant activity of diosmin. The cobalt complex (DCo) was the only that presented antibacterial activity. Additionally, a specific antitumoral effect of diosmin and metal complexes upon human leukemia cells was demonstrated, suggesting an immune regulatory action. The anti-melanoma activity of DCo is 10 times that of diosmin. Metal coordination could be used to improve drug activity and to give direction to a new possibility of clinical use for diosmin. This study was funded by Fundação de Amparo à Pesquisa do Estado de São Paulo, FAPESP (2005/60749-9) and Anhanguera University of São Paulo (UNIAN-SP).
CYTOTOXIC ACTIVITY OPTIMIZATION OF 2,3,4-SUBSTITUTED CHIRAL OXAZOLIDINES IN ORDER TO OBTAIN NOVEL ANTICANCER DRUG CANDIDATE

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Introduction: The low therapeutic index and the many adverse effects are still important challenges to be overcome in the cancer treatment. Our group aim to identify and develop new compounds that are potent and with good selectivity index. During a screening step, a promising anticancer activity of a compound bearing an oxazolidine ring substituted at the 2, 3 and 4 positions was found. The purpose of this study was to synthesize two derivatives of this hit and to evaluate their antiproliferative activity against DAOY, SK-N-BE2 and RD-ES tumor cells lines. Methods: D-serina was protected with tert-butoxycarbonyl and the carboxylic acid was converted to the methyl ester by treatment with iodomethane and potassium carbonate. The reaction of the methyl ester with 2,2-dimethoxypropane and BF$_3$EtO led to the acetonide formation, which was reduced with NaBH$_4$ to alcohol. The alcohol was reacted with 4-nitrophenol in Mitsunobu conditions. The nitrocompound was reduced by catalytic hydrogenation in the presence of Pd-C. A coupling was performed with 4-methylbenzoic or 4-chlorobenzoic acid to provide the designed analogues. Results and discussion: The derivatives exhibited an IC$_{50}$ at low micromolar range. Comparing the activity of chloroamide derivative among the different cell lines, it was observed that this compound was at least 5-fold more potent against the RD-ES cell (IC$_{50}$ 1 µM) when compared to DAOY and SK-N-BE2 cells. Conclusions: The introduction of a chloroamide enhanced the cytotoxic profile against Ewing’s Sarcoma cell line and this compound presents IC$_{50}$ value next to the anticancer drugs being a promising candidate.

Financial Support: BIC UFRGS, CNPq, FAPERGS, CAPES and FAPEMIG.

EVALUATION OF THE AFFINITY AND FUNCTIONAL ACTIVITY OF THE LINS01 COMPOUNDS IN THE HISTAMINE H1-H3 RECEPTORS

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Introduction: The effects of histamine are produced by interaction with four GPCR (H$_1$,H$_2$,H$_3$). The H$_3$ is found predominantly in the CNS, regulating the release of histamine and other neurotransmitters. Ligands of H$_3$ may be useful in the treatment of diseases of the CNS. The 1-[(2,3-dihydro-1-benzofuran-2-yl)methyl]piperazines (LINS01 series) were previously evaluated for H$_1$, H$_2$ and H$_3$ affinity and functional activity, showing selectivity towards H$_3$ rather than H$_2$, as well as antagonistic behavior. In order to have a full panel of the activity of LINS01 compounds in the histamine receptors, the present work aimed to evaluate the affinity and the functional activity at the human H$_1$,H$_2$,H$_3$ through reporter gene assays. Methods: The compounds were synthesized as previously described by us. Functional binding assays were performed using histamine as agonist and mepyramine, IC$_{50}$ 5.6-7.2. Results and discussion: The LINS01 compounds had low or no affinity for the H$_2$ and none of them presented H$_3$ affinity. None of the compounds induced responses at the histamine receptors, suggesting antagonist activity. The preliminary SAR data of the compounds demonstrated that the N-methyl group and substituents on the dihydrobenzofuran nucleus increase the H$_3$ affinity. The methoxylated compound LINS01009 was the most potent (pK$_{a}$ 7.2), while the phenylpiperazine moiety led to the lowest affinity to H$_3$. Conclusions: The results here presented define that LINS01 compounds are novel lead structures to further design of H$_3$ antagonists with good selectivity.

Financial support: The authors are grateful to CNPq (455411/2014-0) and FAPESP (2016/25028-3) for the financial support to the working group and to the fellowship to MFC (FAPESP 2016/23139-2).

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IN SILICO AND IN VITRO EVALUATION OF A SPIRO-ACRIDINE DERIVATIVE WITH POTENTIAL ANTILEISHMANIAL ACTIVITY

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Leishmaniasis comprises neglected infectious-parasitic diseases characterized by the invasion of the parasite into the host macrophage with consequent development of various clinical conditions. Its treatment, which consists mainly on chemotherapy, has many limitations, which makes important the obtainment of new drugs. This study aimed the evaluation of a spiro-acridine derivative (AMTAC01), which shows promising antileishmanial activity, through in silico and in vitro study. The molecular docking study of AMTAC01 was performed using Hyper Chem v. 8.0, in the structures Esterol 14-alpha dimethylase (CYP51, PDB=3L4D), Trypanothione reductase (TryR, PDB=5EBK) and Topoisomerase I (TOP1, PDB=2B9S), previously treated with docking derivative (AMTAC01), which shows promising antileishmanial activity, through Autodock 4.2, generating a score based on ΔG, and an Estimated Inhibitory Constant (Ki). In this study, the required protocol for validation of the methodology was RMSD ≤ 2.0Å. It provided the identity of the interactions and their types, energy and amino acid residues from the active site of the enzyme, treated by the Discovery Studio program. The compound GLDL05 of predicting the binding mode and the affinity of molecules within the active site of a receptor. Based on the Topliss method, 6 new acridine derivatives were synthesized through the coupling of 6,9-dychloro-2-methoxyacridine and thiosemicarbazide derivatives. Structure of Topoisomerase II α complexed with Etoposide and the B-DNA were obtained from the Research Collaboratory of Structure Bioinformatics Protein Data Bank; interaction calculations were performed using the Lamarckian generic algorithm, through Autodock 4.2, generating a score based on ΔG, and an Estimated Inhibitory Constant (Ki). In this study, the required protocol for validation of the methodology was RMSD ≤ 2.0Å. It provided the identity of the interactions and their types, energy and amino acid residues from the active site of the enzyme, treated by the Discovery Studio program. The compound GLDL05...
presented lower ΔG energy (-8.16 kcal/mol), showing higher affinity with Topo IIα, being more active than Etoposide (ΔG= -7.89 kcal/mol). Considering the drug-enzyme-DNA complex, results of ΔG = -12.25 kcal/mol were obtained for GLDL05, presenting higher affinity with the complex than Etoposide (-12.21 kcal/mol). In this sense, the GLDL05 showed important interactions in relation to the reference compound, qualifying it for the continuity of the biological tests.

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INFECTIOUS DISEASES AND DRUG DEVELOPMENT: DEFINITION OF A NEW CHEMICAL SPACE

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Infectious Diseases are caused by pathogenic microorganisms, such as bacteria, viruses, fungi and parasites, and account for about one-third of the causes of mortality worldwide. It represents a serious public health problem, since it affects a large part of the world population, especially in developing countries. In spite of the epidemiological importance of the infectious diseases, there is a low development of new drugs for this therapeutic class. Also, the restricted use of the Lipinski Rule of five (RO5) by pharmaceutical industries also contributed for the limitation on the development of anti-infective agents, since it excludes molecules capable of breaching prokaryote membranes. In this sense, the objective of this study was to evaluate the physical chemical properties of the anti-infective drugs launched to the marked in the last 10 years. To achieve this goal, all approved drugs by the FDA from 2008-2018 were evaluated and compared with the established descriptors. From a total of 69 drugs, 46 were oral drugs and 23 non-oral administered. The results showed that only ten oral drugs obey the RO5, twenty drugs obey Veber, twenty-two follow the Lovering descriptors and only two oral drugs obey the three rules simultaneously. We found that, for all cases, the molecular weight and the TPSA descriptors were violated. We also identified that the oral bioavailability of infectious drugs can redefined by the following new cut-offs, according to the 70th percentile: MW≤900 Da; (cLogP) -1 and 7.5; Hydrogen Bond Acceptors (HBA)≤15; TPSA≤600 Å; and Number of Rotatable Bonds (NRB)≤15.

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WOUND HEALING ACTIVITY IN VITRO FROM RUTIN AND RUTIN ZINC DERIVATIVE COMPLEX

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Flavonoids are secondary plant metabolites that can be used to increase the effectiveness of the healing process by free radical formation inhibition and by inhibiting the activity of enzymes that regulate the inflammatory reaction and the production of collagen. To elucidate the possible mechanisms involved in the wound healing process and to search for new treatment for healing, the present study investigated the influence of the glycosylated flavanoid rutin and its rutin-Zn (II) derivative, on the antimicrobial activity and in the healing process in vitro . The biological parameters evaluated were: determination of the minimum inhibitory concentration (MIC) of flavanoid on strains of Staphylococcus aureus and Escherichia coli; and migration of keratinocytes by the scratch wound method in vitro. The results demonstrated that rutin showed antimicrobial activity against strains of gram positive and negative bacteria. This activity was even higher when using the rutin-Zn, demonstrating an increase in antimicrobial activity by rutin when complexed to zinc ion. The cell migration assay demonstrated that rutin and rutin-Zn at 20.5 and 15.5 μM, respectively, had an effect on the injury of the keratinocyte monolayer. It was shown that after 5 days there was a monolayer repair of 8 mm for rutin and 25 mm for rutin-Zn, indicating the positive effect of zinc coordination on the flavanoid in the healing process in vitro. In this study it was evidenced that the association with zinc increased the biological activity of rutin alone, indicating that metal ions may potentiate the pharmacological effects of this flavanoid.
LINS01 COMPOUNDS AS ANTI-HYPERTENSIVE AGENTS: PRELIMINARY INVESTIGATION ON AN IN VIVO MODEL

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Introduction: The search for novel antihypertensive agents is still a continuous goal in drug design and development. LINS01 compounds have been evaluated by our group as histamine receptor ligands and also in other targets aiming a multitarget therapy to neurodegenerative dementias such as Alzheimer’s disease. Considering that increasing the blood flow in the CNS can improve cognition, the evaluation of the vasodilating effects of such molecules deserves our efforts. We serendipitously observed that one LINS01 molecule (CFP) presented potent vasodilating activity in rat aorta previously. Thus, this work aimed to preliminary evaluate the anti-hypertensive potential of this molecule on a rat model of hypertension. Methods: Spontaneously hypertensive rats (SHR) had their tail blood pressure monitored for 90’ after the i.p. injection of CFP in different doses (0.1-5 mg/kg).1 The baseline blood pressure before injection was used as control (100%), and the activity was measured as % of reduction from control values. The experiments were approved by the Ethics Comitee on Animal Use (CEUA-UNIFESP nº 1012050417). Results and discussion: The CFP compound significantly decreased (p Conclusion: This is the first report of the anti-hypertensive effect of this compound. Considering its activity as anti-inflammatory already evaluated by us, CFP is a potential drug prototype to further optimization in the road of novel multitarget agents against neurodegenerative diseases. Financial support: The authors are grateful to CNPq (455411/2014-0) and FAPESP (2016/25028-3) for the financial support to the JPSF working group and to the fellowship to GABF and MFC (FAPESP 2017/05441-6 and 2016/23139-2).


DIHYDROBENZOFURANYL-PIPERAZINES AS PROCOGNITIVE AGENTS: PRELIMINARY DOPAMINE D2R/D3R PROFILING

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Introduction: Pathological conditions, such as Alzheimer’s and Parkinson’s diseases, vascular dementia and mood/affective disorders improperly affect cognition. The roles of histaminergic and dopaminergic systems are widely known and can be highlighted among the main targets for new procognitive drugs. LINS01 compounds were previously reported1 as histamine H1,R antagonists and some of them are under evaluation in rodent models as procognitive agents. Considering their pharmacological potential and similarities to D3R/D2R ligands described, these compounds were evaluated as ligands of dopamine D3R/D2R receptors. Methods: A set of 13 compounds were synthesized as previously described1 with moderate to good yields. These compounds present the dihydrobenzofuranyl-piperazine core with substituents at 5-position of dihydrobenzofuran ring and at the piperazine nitrogen. The binding assays were performed on human D3R/D2R and measured by [3H]spiperone displacement assays (10 µM, n = 6-15). Haloperidol was used as standard drug. Results and discussion: The compounds showed low to moderate affinities at both D3R and D2R. Compound LINS01006 showed 77% inhibition of radioligand binding, although selectivity was not observed. N-Phenyl compounds LINS01005, LINS01011, LINS01012, LINS01016 showed the higher affinities at D3R (60-80% inhibition), indicating that 1-phenylpiperazine moiety increases the affinity to this receptor subtype. The N-phenyl derivatives also showed lower affinities at D2R (34-45% inhibition) than at D3R, suggesting that N-phenyl group leads to some D2R selectivity. Conclusions: Although the LINS01 compounds are poor D3R/D2R ligands, they can be further optimized to increase the affinity for such receptors, especially taking advantage of the N-phenyl or N-benzyl moiety. Financial support: The authors are grateful to CNPq (455411/2014-0) and FAPESP (2016/25028-3) for the financial support to the JPSF working group and to the fellowship to GABF, MFC and MTV (FAPESP 2017/05441-6; 2016/23139-2; 2016/00195-4).

CYTOTOXIC ACTIVITY OF AN ISOTHIURONUM SALT (IS-MF08) IN A MELANOMA 3D MODEL

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Introduction: Chemoresistance found in patients with melanoma could be explained by the survival of a subpopulation of cells called cancer stem cells (CSC). CSC are a subset of tumor cells with stem-like properties such as the ability of self-renew, initiate tumors and differentiate into a heterogeneous population. The aim of this study was to define the best tumorspheres condition formation and evaluate the potential activity of the isothiouronium salt MF08 (IS-MF08) on CSC population of B16F10.

Methods: Melanospheres were obtained through a nonadhesive 96 well plate coated with agarose with cells plated at low density. Cell surface labeling with CD44 and CD133 was used to identify stem-like cells through confocal and flow cytometry analysis in monolayer culture of B16F10 as well as in melanospheres. After formation, melanospheres were exposed to three different concentrations of IS-MF08 (9 μM, 17.5 μM and 35 μM) and analyzed regarding size, viability and percentage of positive CD44 and CD133 cells.

Results and discussion: The percentage of positive CD133 cells in a 2D culture was 20% and increased up to 76% in melanospheres. For CD44 the increase was higher with a percentage of positive cells from 7% increasing up to 83% in melanospheres. Also, the exposure of 35 μM of IS-MF08 was able to significantly prevent melanosphere grow in 70%.

Conclusion: The melanosphere model is an important tool for in vitro studies of the cytotoxic potential of new anticancer agents since it can enrich the population of CD44 and CD133 positive cells associated with CSC.

SYNTHESIS OF D-GLUCONOLACTONE AND D-GLUCOSE-BASED NEOGLYCOLIPIDS OF INTEREST IN MEDICINAL CHEMISTRY AND PHARMACEUTICAL TECHNOLOGY

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Introduction: the therapy using nanostructures, mainly liposomes, is helpful in treatment of several diseases, especially cancer and infections. Despite their usefulness, the liposomes have limitations, like low circulation time in the bloodstream. Objective: in this study, two dendrimeric neoglycolipids derived from D-gluconolactone (1) and D-glucose (2) were synthesized for incorporation into liposomes to evaluate their influence on the stability and blood circulation time of the corresponding liposomes.

Methods: Initially, esterification of gallic acid (3,4,5-trihydroxybenzoic acid) with methanol was performed. Next, methyl gallate was reacted with N-tert-butoxycarbonyl-3-bromopropylamine, providing the corresponding trisubstituted derivative. Reaction of methyl gallate with propargyl bromide furnished the corresponding tripropargyl derivative. Ester hydrolysis in both cases provided the corresponding trisubstituted gallic acids (key-intermediates 1 and 2, respectively). Next, the synthesis of 2-O-aminoethylcholesterol performed as follows: tosylation of cholesterol followed by reaction with ethyleneglycol furnished the corresponding tripargyl derivative. Tosylation, reaction with sodium azide followed by reduction using LiAlH₄ provided the expected 2-O-aminoethylcholesterol. Reaction of 2-O-aminoethylcholesterol with key-intermediate 1 and 2 furnished the corresponding amides, named amide 1 and amide 2, respectively. To obtain the neoglycolipid 1, the tert-butoxycarbonyl group was removed from amide 1 and the corresponding triamine was coupled to D-gluconolactone. To obtain the neoglycolipid 2, amide 2 was submitted to “click” reaction with 2,3,4,6-tetra-O-acetyl-β-D-glicopyranosyl azide, followed by removal of the protecting groups. Results and discussion: the synthesis of the target molecules was efficient and all compounds were obtained in acceptable to good yields.

Conclusion: two new carbohydrate-based neoglycolipids were successfully prepared using simple synthetic methods.
IN SILICO STUDIES OF EUGENOL DERIVATIVES AS POTENTIAL INHIBITORS OF CYP51 FROM Candida albicans

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Introduction: fungal infections are challenging since the growth of resistance in the last decades certainly surpasses the development of new therapeutic agents. The action of azole-antifungal relies on lanosterol 14α-demethylase (CYP51) inhibition, preventing ergosterol biosynthesis. In this sense, natural-derived products are a viable strategy in the search of new antifungal agents. Eugenol-inspired derivatives are an interesting source of new potential antifungal agents based on reported antifungal properties of natural products. In order to determine the structural bases of the ligand-target interactions, molecular modeling techniques could be applied to design new clinically relevant antifungals. Methods: docking calculations were performed with the protein-ligand complex of CYP51 from C. albicans with GOLD software. The grid region for docking was set over the crystallographic inhibitor. The best docking-scoring solutions were saved and consensual poses used for pose-binding selection. Results and discussion: the redocking calculation was below 2 Å for posaconazole (RMSD = 1.514 Å), validating the docking procedures. The docking analysis of eugenol derivatives indicated a binding pattern similar to the reference inhibitors, fluconazole and posaconazole. Conclusions: The molecular modeling study of known inhibitors allows defining the fundamental binding properties in the search and design of potential antifungal agents against C. albicans.

Acknowledgments: Federal University of Espirito Santo (UFES), Research and Innovation Support Foundation of Espirito Santo (FAPES) and the National Postdoctoral Program (PNPD/Capes).

Financial support: FAPES/CAPES.

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SYNTHESIS OF POTENTIAL INHIBITORS OF THE Plasmodium Falciparum HEXOSES TRANSPORTER (PFHT1) DERIVED FROM D-GLUCOSAMINE

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Introduction: malaria is a serious infectious disease, common in different tropical and subtropical regions, that can lead to death. It is caused by the protozoan Plasmodium sp, Plasmodium falciparum being the species causing the most severe form of the disease. The resistance of the Plasmodium to existing antimalarial agents is considered the greatest challenge in malaria control, emphasizing the need for new treatment regimens. The hexose transport system (PFHT1) of P. falciparum is a potential antimalarial target as the parasite needs glucose as energy source and deprivation of it leads to death of the parasite. As reported in literature, the C-2 substituted D-glucose derivate (2-O-undecenyl-D-glucose) 1, displayed antiplasmodial activity by inhibition of PFHT1. Our group recently carried out the synthesis of an analogue of 1 (N-undecanoyl-D-glucosamine) which also showed activity against P. falciparum strains. Objectives: the aim of this study was the synthesis of N-acyl-D-glucosamine derivatives and the evaluation of their antiplasmodial activity. Methods: reaction of 3- or 4-hydroxybenzaldehyde with allyl bromide furnished the corresponding allylated derivatives which, upon a modified Knoenavenagel reaction afforded 3- or 4-allyloxyxycinnamic acids. Catalytic hydrogenation of these compounds furnished 3- or 4-propoxycinnamic acids. The acid chlorides were obtained by reaction of the appropriate carboxylic acids with oxalyl chloride, under reflux. Reaction of the acid chlorides with D-glucosamine provided the N-acyl-D-glucosamine derivatives. Results and discussions: the four carboxylic acids were obtained in good overall yields, as well as the four N-acyl-D-glucosamine analogs. Conclusions: the proposed synthetic methods were efficient, furnishing the target molecules in satisfactory overall yields.
Introduction: Schistosomiasis treatment relies on a single pharmacological alternative, the praziquantel, which has also been used for prophylaxis, situation which may trigger drug resistance. For this reason, there is an imperative need for new alternatives. N-acylhydrazones are usually explored as good active agents, but the vanillin-related N-acylhydrazones have never been tested by their antiparasitic potential. Herein we report the synthesis of seven analogues, three of them unpublished, and their biological investigation against Schistosoma mansoni. A target fishing study was also performed. Method: The compounds were obtained following classical synthesis. Anthelmintic potential was assessed by observing changes in motor activity and death of adult male worms, as well as by Confocal Laser Scanning Microscopy (CLSM). Cytotoxicity was determined against Vero cells employing MTT viability assay. The target fishing study was performed with Pharmmapper software, considering humans/ not humans targets. BLAST was used to find S. mansoni ortholog proteins. Results and discussion: Compound GPQF-407 exhibited good antischistosomal activity (47.91 µM) with suitable selectivity index (4.14). CLSM study revealed an extensive tegumental destruction after treatment with GPQF-407. Target fishing studies pointed out the Serine-Threonine Kinases, Dihydroorotate Dehydrogenase and Carbonic Anhydrase II as good targets. Conclusion: The GPQF-407 was revealed to be a promising anti-schistosomal agent with good activity associated to good selectivity. This compound exhibits the N-acylhydrazone privileged scaffold, which is easily synthesized on large scales from commercially available materials. This is a desirable combination when regarding new drugs to treat neglected diseases.


SYNTHESIS OF ESTERS OF PACLITAXEL WITH LIPOIC ACID

Introduction: cancer is the second leading cause of deaths worldwide. Several types of cancer are resistant to current chemotherapy. Therefore, the development of new anticancer compounds is urgently needed. Paclitaxel is a potent anticancer that is poorly soluble in water and its formulation contains Chremophor L®, which causes several side effects. Therefore, there is a need for novel derivatives of paclitaxel to overcome the problems of formulation. Nanorods are new nano-systems for drug delivery. Their core is made of gold that binds tightly compounds having thiol groups. Lipoic acid is a natural compound bearing disulfide linkage which upon reduction furnishes two thiol groups. It is used to prepare esters and amides of bioactive compounds to attach to nanorods Objective: this study aimed at synthesizing lipoic esters of paclitaxel to attach to nanorods using two strategies: direct esterification and protecting group-directed esterification. Methods: the synthesis of 2’-O-lipoylpaclitaxel was achieved by reacting paclitaxel with lipoic acid in the presence of N,N’-disopropylcarbodiimide and N,N-dimethylpyridine. The 2’,7-di-O-lipoylpaclitaxel diester was also obtained in this reaction. 7-O-lipoylpaclitaxel was prepared as follows: paclitaxel was reacted with triethylsilyl chloride to furnish 2’-O-triethyilsilylpaclitaxel. Reaction of this compound with lipoic acid as described above furnished the corresponding 7-O-lipoyl ester which, upon reaction with n-tetraethylammonium fluoride gave the 7-O-lipoylpaclitaxel. Results and discussion: the 2’-O-lipoylpaclitaxel monoester of paclitaxel was prepared by direct esterification of paclitaxel, together with the 2’,7-di-O-lipoylpaclitaxel. The 7-O-lipoylpaclitaxel was obtained in three steps from paclitaxel. Conclusion: three new esters of paclitaxel were successfully prepared using well established synthetic methods.
MOLECULAR MODELING STUDIES OF N-ACYLHYDRAZONE ANALOGUES WITH POTENTIAL ACTION ON JAK2

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Introduction: The JAK/STAT pathway is a well known biochemical route which modulates the cell growth, therefore, an enhanced activation of it is related to neoplastic diseases. There are two kinds of JAK2 inhibitors, the I and II types. Type II encompasses potent inhibitors by binding to a allosteric site, instead of the ATP site as the type I ones. Nifuroxazide (NFZ) has been proved to inhibit the JAK2 and, in a previous work, we have demonstrated that it has showed preference to bind at the allosteric site. Herein, we investigated the binding of NFZ analogues to the JAK2, regarding both recognition sites.

Methods: Molecular docking studies were performed with five analogues employing two different JAK2 crystals, in the DFG-in and DFG-out conformations. Redocking studies were performed to establish the protocol.

Results and discussion: As previously observed to the NFZ, its analogues also showed some preference to the allosteric site, which; however, is only available at the DFG-out conformation. GPQF-700 was considered the most promising compound, presenting a recurrent pose with 97% of frequency, and Goldscore and Chemscore values of 54.50 and 29.04, respectively. Hydrogen interactions were observed with Asp994 and Glu989, as well as a cation-pi with Lys882. Moreover, this analog does not present the nitro group, which is frequently associated to toxicity and mutagenicity.

Conclusions: All compounds preferred the allosteric binding site. This is a promising result since the Type II inhibitors are more potent and also more selective since the allosteric site is less conserved among the kinases.

Financial Support: FAPESP 2016/01875-0, CAPES-Bolsa DS.

DEVELOPMENT OF LIPID NANOCARRIERS WITH ANTIBACTERIAL AND ANTIOXIDANT PROPERTIES FOR APPLICATION IN WOUND HEALING

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Population aging, the high incidence of chronic wounds in the elderly and the high costs associated with their treatment motivate the search for innovations to promote wound healing in an attempt to improve patient quality of life and product performance, to simplify treatment and reduce costs. In this study, nanostructured lipid nanocarriers (CLN) were developed using Shea butter and argan oil, and modified with bioadhesive polymers (alginate or chitosan) for the co-encapsulation and co-administration of compounds with antioxidant (vitamin E, quercetin) and antimicrobial activity (tea tree oil). Their characteristics, antimicrobial activity and ability to localize the antioxidants in porcine skin subjected to a linear incision (to mimic barrier damage in wounds) were assessed. Spherical nanoparticles with diameter ~ 300 nm were obtained; zeta potential varied from -23 to +8 mV. Thermogravimetry and differential scanning calorimetry demonstrated that the lipid matrix protected tea tree oil from degradation, and that chitosan-modified nanocarriers were less organized. CLN promoted cutaneous localization of antioxidants in the damaged skin, with 50 to 150-fold more antioxidant delivered into the skin compared to the receptor phase. No differences were observed in their penetration comparing the alginate and chitosan-modified nanocarriers, suggesting that the polymer used and the nanocarrier charge did not affect penetration. The antimicrobial effect of the nanoparticles was evidenced in assays with S. aureus and P. aeruginosa. Based on these results, we conclude that nanoparticles with alginate, antioxidants and tea tree oil may be a new alternative for wound management.

Acknowledgements: Financial support from FAPESP (2013/16617-7) and CAPES (fellowship to S. Fernandez) are greatly appreciated.
ADENYLATE KINASE 3 BINDING SITE MAPPING AND ITS APPLICATION FOR VIRTUAL SCREENING

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Introduction: Adenylate kinase 3 (AK3) is an enzyme located in the mitochondrial matrix involved in purine homeostasis. Recent studies have demonstrated increased levels of AK3 in peripheral blood mononuclear cells of Chronic Lymphocytic Leukemia (CLL) patients. Moreover, silencing AK3 gene has inhibited cell growth, indicating the potential of this enzyme as a therapeutic target in CLL. The aim of this study was to find candidates compounds to inhibitors of AK3. Methods: Protein mapping was performed using FTmap and FTsite web servers and Autogrid software. An analysis of type and frequency of intermolecular interactions was employed to suggest the residues that contribute the most for a ligand binding. Pharmacophoric model construction was achieved using Unity software implemented on Sybyl package. The database applied for virtual screening were FDA Approved, Nubbe Natural Products, Diverse Real Drug-Like Enamine and in-house database. Molecular docking using Surflex software as well as visual analysis were carried out for selection of potential AK3 inhibitors. Results and discussion: Binding sites predicted by FTMap and FTsite were concordant with the substrate binding location. Gly18 and Asp89 were the residues which have contributed the most for hydrogen bonds whereas Lys19 and Ile59 have significantly contributed for hydrophobic interactions. Gly18 and Lys19 are on the GTP binding site. Virtual screening using pharmacophore approach selected 6891 molecules. Through molecular docking and visual analysis, 46 compounds were selected for further investigation. Conclusion: Both protein mapping and pharmacophore model applied in this study was successful for virtual screening. However, the chosen molecules should undergo experimental validation.

Acknowledgments: The authors are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Pro-Reitoria de Pesquisa (PRPq) da Universidade Federal de Minas Gerais, for sponsoring this investigation.

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POPK/PD MODELING AND SIMULATION OF CLIOQUINOL AGAINST Candida albicans AND Microsporum canis

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Introduction: Clioquinol is a drug with several pharmacology activities which oral formulations were withdrawn from the market in 1970 because of its toxic effects that nowadays is a scaffold for antifungals. The aim of this study was PK/PD modeling and simulation for clioquinol, against Candida albicans (ATCC 18804) and Microsporum canis 01 employing an in vitro infection model. Methods: Time-kill curves was perform with C. albicans and M. canis by using multiple MIC values of clioquinol (2 – 8 x MIC). The PKPD parameters were defined by an Eₘₐₓ model. Plasma concentration were extracted from literature (n=18 volunteers) and was used to create a one-compartmental population PK model (Monolix®). The concentrations expected after oral administration of 25 mg q12 or 50 mg q24 of clioquinol were simulated and incorporated to the PKPD model (Phoenix®). Results and discussion: The MIC value was 0.25 µg/mL for the two microorganisms. The mean value of k 0.152 ± 0.012 h⁻¹, EC₅₀ 0.306 ± 0.009 µg/mL and the kₘₐₓ 0.055 ± 0.013 h⁻¹ to C. albicans, and k 0.259 ± 0.226 h⁻¹, EC₅₀ 0.180 ± 0.049 µg/mL and the kₘₐₓ 0.014 ± 0.006 h⁻¹ to M. canis. PopPK model parameters estimates ka 0.617 h⁻¹, V 0.855 L/kg and Cl 0.048 L/kg/h. The simulations showed that the two doses, were able to maintain plasma concentrations above the minimum effective concentration, showing a good potential as antifungal in the doses evaluated. Conclusion: The PK/PD modeling showed a high efficacy of clioquinol against C. albicans and M. canis, and the modeled and simulated data of plasma concentrations contribute to the idea that lower doses may be indicated for the treatment of fungal diseases.

Financial support: FAPERGS/PRONUPEC.
5-NITRO-2-FURFURILIDEN DERIVATES AS POTENT ANTILEISHMANIAL AGENTS: IN VITRO EVALUATION AND STRUCTURE-ACTIVITY RELATIONSHIP ANALYSES

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Leishmaniasis is a neglected disease worldwide, causing over 300 000 deaths/year. New treatments are needed since the current therapy (antimonial pentavalent, amphotericin B and miltefosine) is highly toxic and shows emerging resistance cases. The potential activity against Leishmania infantum promastigotes of a previously reported nitroheterocyclic library of N’-(5-nitrofuran-2-yl)methylene substituted hydrazides, based on nifuroxazide molecular modifications, was investigated. This library containing forty compounds was reported previously against Trypanosoma cruzi. L. infantum promastigotes (LD/1972/WT/P3) were cultured in medium 199, 10% fetal bovine serum, 2% male filtered urine at 25 ºC. Log phase parasites (10⁷/mL) were transferred to 96 wells flat bottom microplates and incubated with 5-nitro-furfuriliden derivatives, miltefosine and amphotericin B (100 – 0.02 µM final concentrations) for 72h at 25 ºC. MTT assay was used to measure parasite viability. Dose response curves and IC₅₀ were determined using Origin Pro 8.0. Activity Cliffs in silico approaches were used to determine SAR and pivotal moieties. The highest anti-promastigote activity was observed for compound #40 with IC₅₀ values of 0.2 µM. Nifuroxazide, amphotericin B and miltefosine showed, respectively, IC₅₀ values of 5.93; 8.58 and 0.02 µM. In conclusion, the performed experiments revealed 5-nitro-furfuriliden scaffold as a promising candidate in the search of Leishmania inhibitors. Activity cliffs analysis reviewed that bulky and hydrophobic 4-benzene substituents are important to activity. Further analyses with intracellular amastigotes are to be conducted to confirm leishmanicidal properties.

Acknowledgments: CAPES, USP.

DRUG REPURPOSING FOR THE TREATMENT OF THE ZIKA VIRUS FEVER: VIRTUAL SCREENING AGAINST THE NS1 PROTEIN

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Introduction: Zika’s recent outbreak in the Americas and serious complications (e.g. microcephaly and Guillain-Barré syndrome) have recently brought attention to the disease. Currently there are no specific drugs for the Zika treatment. Hence, the non-structural protein 1 (NS1) has been studied as a possible target. It is a glycoprotein involved in the synthesis of the viral RNA and is present as a monomer in the virus. The protein dimerization is crucial for it to bind to the endoplasmic reticulum membrane, acting on the flaviviral replication complex. This work aims to perform computational evaluation of possible binding sites of the NS1 and its inhibition of dimerization or membrane binding by FDA-approved drugs, as a drug repurposing investigation. Methods: Possible binding pockets in the NS1 protein were defined using the webserver DoGSiteScorer. For the virtual screening we adopted three different docking programs (AutoDock4.2, AutoDock Vina and GOLD) against three different binding pockets, in a total of nine calculations, using the e-Drug3D database. Results and discussion: Three pockets were selected based on their locations and druggability scores. Among the best results from the virtual screening against those pockets were beta-adrenergics, antibiotics and anti-Hepatitis C drugs. Those were chosen based on their scoring functions, but also feasibility in usage against the Zika disease, mainly by pregnant women. A number of drugs showed similar conformations by all programs. Conclusion: This study unravels a possible therapy against the Zika disease, in vitro and in vivo tests should be done to validate these results.

Financial support and acknowledgements: CNPq, CAPES, FAPERJ.
EVALUATION OF ISATIN DERIVATIVES AS POTENTIAL GSK-3 INHIBITORS

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Introduction: Glycogen Synthase Kinase-3 (GSK-3), a serine/threonine kinase, has two closely related isoforms, GSK-3β and GSK-3α. A number of different chemical compounds have been identified as inhibitors of GSK-3β, e.g., indole-based compounds started from isatin. Methods: The triazolic derivatives of isatin were obtained by 1,3-Dipolar Cycloaddition Reaction, in the presence of copper sulphate, sodium ascorbate, DMF and irradiation by microwave. The N-alkylated derivatives of isatin were obtained by bimolecular nucleophilic substitution in the presence of commercial bromides, K2CO3 and DMF. The enzymatic assay to the evaluation of GSK-3β potential inhibition of isatin derivatives involves the ADP-Glo™ Kinase commercial assay, a luminescent kinase assay which measures ADP formed from a kinase reaction, wherein the ADP is converted to ATP. All reagents were purchased from Promega, LLC. Results: Ten novel N-alkylated and triazolic derivatives of isatin have been obtained, characterized by 1H NMR, 13C NMR, HMBC, COSY, IR and are being tested as inhibitors of GSK-3β. 1H NMR analysis of 1-((1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)indoline-2,3-dione, for example, demonstrated the presence of hydrogens of the methoxyl group in δ 3.80(s), the hydrogens characteristic of isatin in δ 7.57(d), δ 7.07-7.16(m), δ 7.65(t) and δ 7.22(d), as well as the triazole ring hydrogen in δ 8.50 (s) and CH3 group evidenced in δ 5.04(s). The four aromatic hydrogens of anisole substituent were demonstrated in the region of δ 7.07-7.57. Conclusion: The evaluation of ten novel isatin derivatives as inhibitors of GSK-3β is ongoing. Acknowledgments: This work was supported by FAPES and UFES.

IN VITRO EVALUATION OF THE CYTOTOXIC ACTIVITY OF HISTONES DEACETYLASE INHIBITORS IN CHRONIC MYELOID LEUKEMIA MODEL

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Introduction: Leukemia is a malignant disease that originates in the bone marrow, where blood cells are produced. Chemotherapy treatment is one of the alternatives to improve patient survival. However, the main problems associated with the treatment of leukemias are the high rates of systemic toxicities and the increased resistance to the therapeutic arsenal available. In this context, the search for new compounds with potential antitumor action is justified and becomes relevant. In the present work the cytotoxic activity of 7 new synthetic compounds of HDAC inhibitors was evaluated. Methods: The cytotoxic profiles were determined by the in vitro assay of 3- (4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-tetrazolium (MTT) in cell line K562 (chronic myeloid leukemia) and PBMC (mononuclear cell peripheral blood). Induction of apoptosis was assessed by flow cytometry using annexin V / propidium iodide. Results and discussion: The compounds IDH-4, IDH-5, IDH-6 and IDH-7 were the most active (35.40, 40.30, 28.45 and 30.70 μM respectively) and selective (IDH-48) and HDI-7 (2.98) for K562 in relation to the imatinib chemotherapeutic control (37.77 μM). All of these induced apoptosis in the tested strains. Conclusion: Thus, investigating the mechanism of action of the compounds, we have observed results that suggest that they are potential cytotoxic and selective molecules for CML cell line. Acknowledgments: The authors are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Pro-Reitoria de Pesquisa (PRPq) da Universidade Federal de Minas Gerais, for sponsoring this investigation.
IN VITRO EVALUATION OF THE CYTOTOXIC ACTIVITY OF HISTONE DEACETYLASE INHIBITORS IN ACUTE MYELOID LEUKEMIA

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Introduction: Inhibitors of histone deacetylase (HDACIs) have been increasingly studied because they present as characteristic the ability to alter the acetylation status of histones and non-histone proteins, regulating several cellular events such as differentiation, cellular survival and apoptosis in tumor cells, which make them potential powerful antitumor agents. Thus, scientific efforts have strengthened the search for new HDAC inhibitors with novel features and the selective isoform is one of the most promising therapeutic targets for cancer treatment. In the present work the cytotoxic activity of seven new synthetic HDAC inhibitor compounds was evaluated. Methods: The cytotoxic profiles were determined by the in vitro assay of 3- (4,5-dimethyl-2-thiazolyl) -2,5-diphenyl-tetrazolium (MTT) in the THP1 cell line (acute monocytic leukemia - ATCC TIB-202) and PBMC (mononuclear cell peripheral blood - COEP-02177612.0.0000.5149/Ethics approval). Induction of apoptosis was assessed by flow cytometry using annexin V/propidium iodide. Results and discussion: The compounds IDH-4, IDH-5, IDH-6 and IDH-7 were the most active (20, 14, 24, 50, 9,20 and 13,55 μM, respectively) and selective (IDH-6, 67) and IDH-7 (6.70)) for THP1 cell line. All of these induced apoptosis in the tested strains. Conclusion: Thus, investigating the mechanism of action of the compounds, we have observed results that suggest that they are potential cytotoxic and selective molecules for AML in vitro model.

Acknowledgments: The authors are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

CYTOTOXIC ACTIVITY OF 3-ALKYLPYRIDINE ALKALOIDS IN CHRONIC MYELOID LEUKEMIA IN VITRO MODEL

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Introduction: Chronic Myeloid Leukemia (CML) is a chronic myeloproliferative pathology arising from the clonal expansion of transformed hematopoietic stem cells, and is characterized by the presence of a specific cytogenetic abnormality, the Philadelphia chromosome. This chromosome is the product of the t (9; 22) translocation (q34; q11) resulting in a hybrid BCR-ABL gene, which encodes a BCR-ABL chimeric oncoprotein with tyrosine kinase activity. Regarding CML, research has focused on the development of new drugs capable of combating imatinib-resistant BCR-ABL clones and, consequently, reducing the risk of resistance. In the present work the cytotoxic activity of 16 new synthetic analogs of 3-alkylpyridine alkaloids was evaluated. Methods: The cytotoxic profiles were determined by the in vitro assay of 3- (4,5-dimethyl-2-thiazolyl) -2,5-diphenyl-tetrazolium (MTT) in the K562 cell line (chronic myeloid leukemia - ATCC CCL-243) and PBMC (mononuclear cell peripheral blood - COEP-02177612.0.0000.5149/ Ethics approval). Induction of apoptosis was assessed by flow cytometry using annexin V/propidium iodide. Results and discussion: The compounds SCN-002 (21.66 μM) and SCN-003 (15.37 μM) were the most active and selective for K562, compared to imatinib (34.58 μM). All of these induced apoptosis in the tested line. Conclusion: Thus, investigating the mechanism of action of the compounds suggests that they are cytotoxic compounds against leukemic line. Thus, data presented in this work indicate that 3-alkylpyridine alkaloid analogs are a potential class of compounds with in vitro cytotoxic action.

Acknowledgments: The authors are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), for sponsoring this investigation.
STUDY OF IN VITRO CYTOTOXIC ACTIVITY OF 3-ALKYL PYRIDINE ALKALOIDS IN ACUTE MYELOID LEUKEMIA

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Introduction: Acute Myeloid Leukemia (AML) is an aggressive malignant disease of the hematopoietic system, characterized by the uncontrolled proliferation of abnormal blastic cells of the granulocytic lineage and by the decrease of normal blood cell production. Considering the current challenges observed in AML, the limited therapeutic alternatives and many side effects of chemotherapy as well as the heterogeneity of patient subgroups justify the development of compounds based on new classes of molecules for the treatment of this disease. In the present work the cytotoxic activity of 16 new synthetic analogs of 3-alkylpyridine alkaloids was evaluated.

Methods: The cytotoxic profiles were determined by the in vitro assay of 3- (4,5-dimethyl-2-thiazolyl) -2,5-diphenyl-tetrazolium (MTT) in the THP1 cell line (acute monocytic leukemia - ATCC TIB-202) and PBMC (mononuclear cell peripheral blood - COEP-02177612.0.0000.5149/Ethics approval). Induction of apoptosis was assessed by flow cytometry using annexin V/propidium iodide.

Results and discussion: The compounds THP-003, OH-002, OH-003 and CHO-004 were the most active (33.53, 22.11, 27.19 and 37.99 μM, respectively) and selective for THP1 in which they were comparable to the standard used (40.75 μM), cytarabine, compound already used as chemotherapy. All of these induced apoptosis in the tested line.

Conclusion: The investigation of the mechanism of action of these compounds suggests that they are potential cytotoxic and selective molecules for leukemic cell line.

Acknowledgments: The authors are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), for sponsoring this investigation.

EVALUATION OF ANTITUMORAL EFFECT OF ARTEPILLIN C IN BREAST CANCER CELLS LINES

ID: 353

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Breast cancer is the most common type of cancer among women in the world and has a limited treatment with several adverse effects. Artepillin C (3,5-diprenyl-4-hydroxycinnamic acid) is one of the main constituents of Brazilian propolis and has shown several activities, including against various types of cancers. The present study aims to evaluate the antitumor potential of Artepillin C in breast cancer cells (MCF-7 and MDA-MB-231). Cells viability was assessed by the MTT assay and morphological changes were observed by common optic microscopy. The long-term cytotoxicity was performed by clonogenic assay and cells migration was determined by the wound-healing assay. Citotoxicity was more evident in MCF-7 (IC₅₀ 48h, 60μM), with a tumor selectivity index (TSI) of 1.41 compared with MDA-MB-231 (IC₅₀ 48h, 90 μM; TSI of 0.94). Morphology of tumor cells were altered after 48h of treatment in a dose-dependent manner, with decrease of the confluence, cytoplasmic vacuolization and elongation, appearing of round cells, indicating cell detachment and death. The clonogenic potential in both tumor cells was reduced significantly also in a dose-dependent manner, in the evaluated period (7 days). Artepillin C (IC₅₀ and IC₃₀) were able to reduce significantly the cell migration in the two cancer cell lines tested, compared to those not receiving treatment. Artepillin C has demonstrated antitumor potential in breast cancer cells tested, suggesting new possible therapeutic strategies or adjuvants in the treatment of breast tumors.

Financial suport: This work was supported by grants from Brazilian Government (PROCAD 88881.068413/2014-01).
SYNTHESIS, CHARACTERIZATION AND EVALUATION OF THE ANTITUMORAL POTENTIAL OF ISOTHIOSEMICARBAZIDE-ACRIDINE DERIVATIVES, THROUGH MOLECULAR DOCKING STUDIES WITH TOPO II COMPLEXED WITH DNA

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Topoisomerase II alpha (Topo IIα) is one of the essential enzymes involved in cellular processes and when inhibited prevents cell multiplication. In this context, acridine derivatives are extensively studied for intercalating DNA and inhibiting Topo IIα. The present study aimed to synthesize, characterize and evaluate the antitumor potential of isothiosemicarbazide-acridine derivatives (WCM series), applying the molecular docking technique with the Topo IIα complexed with DNA. The docking was done through the AutoDock Tools (ADT) 1.5.6 program. The compounds previously synthesized were physicochemically and structurally characterized by 1H NMR, infrared (IR) and mass spectrometry (MS). An initial screening with 16 compounds was performed through the docking. For the synthesis, 6 compounds were selected, in which WCM06, presenting ΔG= -11.29 kcal/mol and Ki= 5.26 nM, was the one that most approached the positive control (Etoposide). In 1H NMR spectra it was possible to identify, for example, OCH3 (2.50 ppm) and NH (12.76 ppm). In IV, the characteristic band of C=N bond can be identified, suggesting the formation of an imine, and the characteristic band of connection C=S. In MS, it was identified at 274 m/z as the base peak. It was observed in the docking that the compounds containing the disubstituted acridinic nucleus strongly inhibited Topo IIα. This can be explained by the presence of OCH3 in the nucleus, favoring a conformation of greater interaction with the DNA, and the isothiosemicarbazide portion with Topo IIα. The selected compounds presented yields above 50% and had their structures characterized and proven.

Support: UEPB/CNPq.

STATISTICAL ANALYSIS OF PHYSICOCHEMICAL PROPERTIES OF ANTIBACTERIAL COMPOUNDS AGAINST METHICILLIN-RESISTENT Staphylococcus aureus (MRSA)

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Introduction: Currently, MRSA organisms have been shown to be a significant problem in world health, and it was included in WHO’s health emergency highlights. MRSA infections cause a large number of morbidity and mortality in hospital and it’s prevalence acquired in brazilian hospitals is about 54%. Thus, there is a necessity to control the infection by these organisms in a context of restricted options of pharmacotherapy what makes fundamental the search for new drugs active against MRSA.

Methods: ChEMBL database entries for compounds with activity against S. aureus was filtered using Knime Analytics Platform applying some criteria. The compounds were divided in active/inactive considering a 10 μM cutoff for MIC-values. Physical properties were calculated using PaDEL Descriptor and statistical analysis were carried to compare actives/inactives. Results: The parameters were classified as logical (duplicate, missing values), chemical (mixtures, salts, inorganics-compounds) and biological (organisms, strains, methicillin-susceptibility). Number of hydrogen bond acceptors/donors and rotatable bonds, logP, topological polar surface area, sp3 carbon fraction and molar weight were calculated with PaDEL. It was observed a notably distinction between the active/inactive molecules by tPSA values, where active molecules have predominantly about 150Å2 and inactive molecules has major about the values 50-75Å2. Furthermore, active compounds are heavier (MW about 500g/mol) than inactives ones, likewise the number of HBD is higher in active compounds.

Conclusion: The physicochemical proprieties’ analysis of active/inactive molecules against MRSA showed distinctions that will be useful in the development of machine learning techniques based-models, which will be employed in new antibacterials virtual-selection.

Financial Support: CNPq, FAPEMIG, UFMG.
SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF SOME NEW ISATIN DERIVATIVES

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Introduction: Isatin (1H-indole-2,3-dione) and its analog, are versatile substrates which acts as a precursor for large number of pharmacologically active compounds. Isatin and its derivatives demonstrate antibacterial, anticonvulsant, antiinflammatory, analgesic, antifungal, antiviral, and anticancer properties. Thus having a remarkable role in the synthesis of different heterocyclic compound. **AIM.** The aim of this work is synthesis, characterization and evaluation of antibacterial activity of novel N-alkylated and triazolic derivatives of isatin. **Methods:** Synthesis. The N-alkylated derivatives of isatin were obtained by bimolecular nucleophilic substitution (SN₂) in the presence of commercial bromides, K₂CO₃ and DMF. The triazolic derivatives of isatin were obtained by Cu(I)-Catalyzed Huisgen Azide-Alkyne 1,3-Dipolar Cycloaddition Reaction, in the presence of copper sulphate (CuSO₄), sodium ascorbate, DMF and irradiation by microwave at 150 W, 70 °C for 15 minutes. The samples were submitted to broth microdilution test (MD) in order to determine the minimum inhibitory concentration (MIC) against strains of *Staphylococcus aureus*/methicillin-resistant, S. coagulase negative/methicillin-resistant, Vancomycin-resistance enterococcus, Nonfermenting Gram-negative Bacilli/carbapenemes + *Klebsiella pneumoniae*. **Results:** The compounds obtained: 1-(1,3-dioxoisindolin-2-yl) methyl)indoline-2,3-dione, 1-(2-(phenylsulfonyl)methyl)benzyl)indoline-2,3-dione, 1-(1-(2-(phenylsulfonyl)methyl)benzyl)-1H-1,2,3-triazol-4-yl) methyl)indoline-2,3-dione and 4-((4-(2,3-dioxoisindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzoic acid, have been confirmed by ^1^H NMR, ^1^3C NMR, HMBC, COSY and IR. **Conclusion:** The compounds were obtained, characterized and the evaluation of their antibacterial activity is ongoing.

Acknowledgments: This work was supported by FAPES and UFES.

PLANNING, SYNTHESIS AND CITOTOXICITY INVESTIGATION OF A SERIES OF ISOXAZOLYL-SULFONAMIDES

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Introduction: A series of 20 isoxazolyl-sulfonamides were planned and synthetized aiming to deepen an ongoing structure-activity relationship study on isoxazole derivatives. In previous works, we evaluated the biological potential and drug likeness-related properties of these compounds using in silico tools. Ahead of assaying the compounds against the predicted biological activities, we evaluated and present now their cytotoxicity against A549, HCT-8, VERO and THP-1 cells. Ideally, the compounds should present low toxicity what would result in high selective indexes for the proposed biological activities (trypanocidal, leishmanicidal, anti HSV-1 and antimicrobial). **Methods:** The compounds were synthesized through 1,3-dipolar cycloaddition followed by S-N coupling between the isoxazole derivative and different sulfonyl chlorides. Their cytotoxicity at the maximum concentration of 500 µM was assessed using either sulforhodamine B or MTT. **Results and discussion:** Five series of four compounds each were synthesized varying substituents at the two phenyl rings. The yield of the reactions was satisfactory (from 17 to 62%) and the compounds were purified via column chromatography and characterized by HRMS, ^1^H and ^1^3C NMR. The compounds were evaluated against tumoral human cell lines (A549, HCT-8) and non-tumoral cell lines (VERO, THP-1). Out of twenty compounds, four decreased cell viability of, at least, one cell line at 500 µM. However, their CC₅₀ values ranged from 327.3 µM to 436.9 µM and the compounds can be considered as only slightly cytotoxic.

**Conclusions:** Twenty isoxazolyl-sulfonamides were synthesized in satisfactory yields. As they show low cytotoxicity, other biological activities will be next evaluated.

Acknowledgments: FAPESC, CAPES, CNPq, PPGFAR/UFSC
COUPLING OF A TRYPANOCIDAL COMPOUND TO AMINO ACIDS AS A STRATEGY TO INCREASE SOLUBILITY: IN SILICO DRUGLIKENESS EVALUATION

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Introduction: Our research group has been investigating heterocyclic compounds with trypanocidal activity, among them, isoxazole derivatives have been shown to be effective, nevertheless they have low aqueous solubility. To increase the solubility of the compounds, we adopted the strategy of coupling amino acids to the structure, however it may negatively impact bioavailability. In this work we are going to evaluate physicochemical descriptors of the designed compounds aiming to predict their oral bioavailability.

Methods: The structures were drawn in the software Chemdraw 12.0, with the 20 amino acids individually attached to the isoxazole compound 1. Their physicochemical properties were calculated using the software Osiris Data Warrior 4.7.3.

Results and discussion: The criteria used to predict bioavailability of the compounds are based on the Lipinski (Logp. Conclusion: In silico analysis showed that all compounds, except those linked to arginine and lysine, are predicted to have a good oral availability. This encourages us to adopt the amino acid coupling strategy as an option to increase the aqueous solubility of trypanocidal compounds.

Acknowledgements: The authors would like to thank FAPESC, CNPq and PPGFAR/UFSC for the financial support.

NEW ANTITUMORAL AZIRIDINES AS DNA MINOR GROOVE BINDER

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Introduction: Drug-DNA interaction has been of great importance since the second half of the 20th century since small molecules can modulate and interfere with the DNA functions. Since aziridines are known as alkylating agents, we studied how 2-phenyl-1-alkyl-aziridines, with crescent-like shape conformation, may interact with TNBC cells. Methods: Synthesis of aziridines involved intramolecular cyclization of the β-amino alcohols, which were obtained by aminolysis of epoxide starting material. This approach led to the development of a homolog series of both N-substituted aziridines and β-amino alcohols. These compounds were compared to cisplatin and screened against MCF-10 (healthy breast tissue), MCF-7 (hormone-responsive breast cancer) and MB-231 (triple negative breast cancer). Cell death was investigated via flow cytometry and the mechanism of action was studied via fluorescence assay with ct-DNA. computation docking was performed to verify the viability of the interactions found.

Results: Synthesized compounds were tested preliminary SAR data was defined. Novel compounds showed higher activity and higher selective index towards TNBC cells compared to cisplatin. The compounds presented an apoptotic profile, and due to the exclusively hyperchromic effect found on these drugs-DNA interactions in the UV-spectra, it was suggested a minor groove binding. Molecular docking was performed and the results were in accordance with the experimental assay. Conclusion: The new structures obtained showed higher activity towards TNBC cells and less toxicity in healthy cells than cisplatin, by interacting with DNA minor groove, a new type of mechanism of action for aziridines.
SEMI-SYNTHESIS OF ELATOL AND ISOOBTUSOL DERIVATIVES

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Introduction: Elatol (1) and isoobtusol (2) are halogenated chamigrane sesquiterpenes found in the red alga Laurencia dendroidea J. Agardh (Rhodomelaceae). Both compounds showed a variety of biological activities such as cytotoxic activities and antimicrobial activity. However, their lipophilicity is a limiting factor for pharmacological assays. With the aim to obtain more hydrophilic derivatives, this work was focused on semi-synthesis of glycosylated elatol and isoobtusol derivatives. Methods: Elatol (1) and isoobtusol (2) were isolated from the dichloromethane/methanol 2:1 (v/v) extract of L. dendroidea through successive chromatographic methods. The O-glycosylation reactions were conducted following the methodology of imidates reactions, varying the monosaccharide donors, in the presence of TMSOTf as catalyst in anhydrous conditions. Results: The natural acceptors 1 and 2 were isolated with good yields. The semi-synthesis reactions provide six glycosylated derivatives, containing as monosaccharide units glucose, galactose and arabinose. The yield of the reactions was modest (ranging from 11, 1% to 45, 4%) and the compounds were purified via column chromatography and characterized by 1H and 13C NMR spectroscopy. Conclusions: The O-glycosylation reactions using these conditions afforded the glycosylated derivatives of elatol (1) and isoobtusol (2) with modest yields.

EXPLORING THE PHYSICAL CHEMICAL PROPERTIES OF ANTICANCER DRUGS

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Introduction: The number of chronic non-infectious diseases, such as cardiovascular diseases, cancer, lung problems and diabetes, were the main responsible for 80.7% of deaths in 2016. Among these pathologies, cancer is currently the second leading cause of death in the world becoming prevalent in less developed regions. Due to the great demand for new antineoplastic drugs, many pharmaceutical and biotechnology companies invested in new oncology therapies during the last 25 years leading to the development of a total of 180 new molecular entities approved in the period 1951 to 2013. Objectives: In this view, the objective of the present study is to investigate the chemical space of antineoplastic drugs since this class of biomolecules does not fit the physico-chemical described for small molecules. Methods: In the present study, we investigated a total of small 250 molecules approved as an anticancer drug in the ChemBL database. Later, we analized the physical chemical and strucutral properties that can influence the oral administration or the mechanism of action of these drugs. Results: Our preliminary results show that the molecular weight (779.6 Da), topological polar surface area (195.5 Å), number of rotatable bonds (14) and hydrogen bond acceptors (14) present higher values compared to the usual physical chemical filters for oral administration of drugs. Unexpectedly, LogP (5), hydrogen bond donors (5) present the same cut offs stablished by Lipinski. Conclusion: Thus, our preliminary results shows that the chemical space of anticancer drugs area broadner in many aspects and needs further studies in order to identify the chemical requirements of oral biovaibility.
MOLECULAR DOCKING STUDY OF ACRIDINE DERIVATIVE WITH 2-HYDROXYPROPYL-BETA-CYCLODEXTRIN AND BETA-CYCLODEXTRIN

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Introduction and objective: Acridines derivatives appear as an class important of synthetic chemical compounds, since their various biological activities have been described in the literature, but these compounds have poor solubility. Thus, the objective of this work was to show through study of docking the increment of solubility with two kinds of cyclodextrins. Materials and methods: Molecular modeling was used to elucidate the specific aspects of intermolecular interaction and calculate the interaction energy among the guest AMTAC-02 and the hosts β-CD and HP-β-CD through. Two aspects of synthesis of derivatives were taken into consideration: regioselective and formation of homologous derivatives with lower and higher molar substitution (MS) ratio are also formed in addition to the product. The values of intermolecular interaction energy for host:guest inclusion complexes were calculated using Autodock VINA software. Results and conclusion: The best coupling solution for the β-CD: AMTAC-02 complex coupling showed energy of -6.60 kcal / mol, 3 hydrogen bonds (HB) of 2.9, 2.9, 3.0 Å and 9 contacts hydrophobic (HC), while the best coupling solution for HP-β-CD: AMTAC-02 was the anchoring energy of -7.9 kcal / mol, 3 HB of 3.1, 3.1, 3.3 Å and 13 HC. The complexes formed with the HP-β-CD host are more energetically favorable than those with β-CD, for both hosts. Hydroxypropyl substituents (HP) play an important role in the intermolecular interaction difference between these complexes, increasing the hydrophobic contacts and favoring the stabilization of the complexes formed with HP-β-CD.

Support or studentship: CAPES, UFPE.

ANTI-BIOFILM ACTIVITY OF NITROFURANS DERIVATIVES AGAINST DIFFERENT CANDIDA SPECIES

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Objectives: The increase in the incidence of fungal infections has advanced significantly and epidemiological data show that Candida yeasts are the main responsible for fungal infections in humans, being Candida albicans the most important pathogen and most prevalent. Therapies for the treatment of infectious processes caused by fungi have found a series of problems such as the growing evolution of antimicrobial resistance, the limited number of available drugs and side effects. In this context, the aimed of this study was verify the antifungal activity and anti- biofilm of 12 nitrofuran derivatives against ATCC strains of C. albicans, C. krusei, C. glabrata and C. parapsilosis. Methods: Susceptibility tests were performed according to the document M27- A3 - CLSI (2008). The biofilms were formed in RPMI broth supplemented with glucose 2% and metabolic activity was determined by the XTT reduction assay. For the characterization of biofilm formation was used the scanning electron microscopy (SEM). Lastly it was evaluated the anti-biofilm activity of nitrofuran derivatives. Results: The best minimum inhibitory concentration values (MIC) were obtained for L7CF113 and L7CF165 compounds. The L7CF113 was able to reduce 75% of the metabolic activity in concentrations equal to or higher than 250 mg /L for C. albicans and C. glabrata biofilms. The reduction was approximately 56% in concentrations equal to or higher than 31.25 mg/L to C. parapsilosis biofilm. In relation to the compound L7CF165 was verified a reduction of 82% of metabolic activity in concentrations equal to or higher than 250 mg /L for C. albicans and in C. parapsilosis biofilm the reduction was approximately 56% in concentrations equal to or higher than 125 mg/L. Conclusions: These results showed that the nitrofuran derivatives, L7CF113 and L7CF165, appear as promising therapeutic molecules.

Financial Support and acknowledgements: FAPESP, CNPq, CAPES, PADC-FCF UNESP.
IN VITRO AND IN VIVO EFFICACY AND TOXICITY OF NONYL 3,4-DIHYDROXYBENZOATE, A POTENT COMPOUND AGAINST Dermatophytes Biofilms

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Objectives: This study aimed to verify the in vitro susceptibility of nonyl 3,4-dihydroxybenzoate free and into nanostructured lipid systems (NLS) against planktonic cells and biofilms of dermatophytes, as well as the efficacy and toxicity in a murine model of dermatophytosis and alternative methods. In addition, the probable mechanism of action was evaluated.

Methods: The preformed biofilms and planktonic cells of T. rubrum and T. mentagrophytes were treated with synthetic antifungal drugs and nonyl 3,4-dihydroxybenzoate. The metabolic activities were determined by XTT reduction assay, by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The NLS form was evaluated according the document M38-A2 (CLSI (2008). The efficacy of the compound was evaluated in wild type (WT) C57BL/6 mice and the toxicity was evaluated in HaCaT cell lines by the sulforhodamine B method and in C. elegans model. Results: T. rubrum and T. mentagrophytes biofilms were significantly more resistant to fluconazole, griseofulvin and terbinafine than planktonic cells (pin vivo testing in C. elegans model, with increased the survival of larvae. Nonyl caused enlargement of the vacuoles, besides derangement and formation of pores in the plasma membrane, similar to amphotericin B. Conclusions: These findings show that nonyl 3,4-dihydroxybenzoate may be a promising antifungal.

Funding: CNPq, CAPES and FAPESP.
Section
Natural Products and Toxicology
SEMI-SOLID FORMULATIONS CONTAINING HYDROETHANOLIC EXTRACT OF Schinus terebinthifolia REDUCES LESIONS CAUSED BY Herpes simplex VIRUS TYPE 1

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Herpes simplex virus type 1 (HSV-1) infections are very common in the population and the recurrent episodes are usually painful and long lasting and may cause discomfort and embarrassment to the individual because of the appearance of the lesions. The intensive use of therapeutic drugs to treat these infections has led to undesirable effects, such as drug-resistant strains and toxicity. Therefore, the search for new treatments for HSV infection is needed. In the present study, semi-solid formulations (ointment and emulsion) that contained a crude hydroethanolic extract (CHE) from S. terebinthifolia at 2% and 5% were developed and in vivo therapeutic efficacy of these formulations was investigated on Balb/c mice (study approved by the Animal Ethics Committee of UEM, number 018/2013). The negative control (untreated) and positive control (acyclovir treatment) groups were included in the study. Treatments with the ointments or emulsions containing CHE effectively reduced herpetic lesions, with a significant difference from the untreated group. Herpetic lesions in the animals that were treated with the formulations that contained the extract took longer to appear, and the lesions were softer and resolved more quickly. Significant differences were also observed between the ointment and emulsion. The treatment with CHE ointments showed to be more efficient than CHE emulsions. In addition, treatment with CHE ointments did not significantly differ from the positive control group that was treated with acyclovir, suggesting that formulations containing the CHE may be a potential candidate for topical treatment of herpetic lesions.

Acknowledgments: CAPES, CNPq, Fundação Araucária, FINEP, Programa de Pós-graduação em Ciências Farmacêuticas (UEM) and Programa de Pós-graduação em Biologia Vegetal (UFMS).

ISOLATION OF FLAVONOLS FROM Erythroxylum simonis PLOWMAN (ERYTHROXYLACEAE) AND INVESTIGATION OF THEIR IMMUNOMODULATORY ACTIVITY

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Introduction: Erythroxylum simonis Plowman, presents distribution in some states of northeastern Brazil. Objectives: To study phytochemistry and to analyze the immunomodulatory potential of isolated compounds from aerial parts of the species. Methods: The plant powder was macerated in 95% ethanol and then the liquid-liquid partition of the extract was performed. The ethyl acetate phase was fractionated by column chromatography using Sephadex LH-20 and 19 fractions was obtained (ESFA 1-2 to ESFA 44). The fraction ESFA 15 was analyzed by HPLC using a C-18 reversed phase column. The identification of compounds was performed by mass spectrometry and NMR (¹H and ¹³C). To evaluate the immunomodulatory activity of the isolated compounds, female mice were stimulated with thioglycollate in the peritoneal cavity to obtain macrophages. Determination of cell viability was performed by the MTT assay. The effect on the production of nitric oxide (NO) was studied in vitro by the Griess reaction method. The modulating effect, of these compounds, on the levels of TNF-α and IL-6 cytokines, was analyzed by ELISA. This research has been appreciated by the Ethnic Committee from the Federal University of Paraiba (N°125/2016). Results: The chromatographic fractionation of E. simonis resulted in the isolation of quercetin-3-sambubioside and canferol-3-sambubioside. None of the flavonol tested were able to reduce cell viability or to interfere in the production of NO and the cytokines TNF-α and IL-6 produced by macrophages stimulated with bacterial lipopolysaccharide. Conclusions: The results contributed to the phytochemical and pharmacological knowledge of the species E. simonis and its genus.
ANTIBACTERIAL ACTIVITY OF Hesperozygis ringens (Benth.) Epling AGAINST PATHOGENIC BACTERIA OF FISH

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Introduction: Natural products are promising sources of research due to their biological activities. The species Hesperozygis ringens (Benth.) Epling, known as “espanta-pulga”, has been studied because of its pharmacological potential in pisciculture. The present work aims to evaluate the \textit{in vitro} antibacterial activity of the hexane and ethanolic extracts of leaves and branches of \textit{H. ringens} against the \textit{Raotella ornithinolytica} and \textit{Citrobacter freundii} strains. Methods: The leaves and branches were collected in Santa Maria, RS, Brazil (exsicata in HDCF 6720, UFSM) and were dried, grounded and extracted sequentially with hexane and ethanol. Both extracts were concentrated and lyophilized and had their antibacterial activity (6400 - 3.125 μg/mL) against \textit{R. ornithinolytica} and \textit{C. freundii} evaluated. Assays were performed at bacterial concentration of 1x10\textsuperscript{5} CFU/mL by micro-dilution in Müller-Hinton broth, according to protocol VET04-A2 (CLSI, 2014). The minimum inhibitory concentration (MIC) was determined using resazurin, where as the determination of the minimal bactericidal concentration (MBC) occurred by subcultivating in Müller-Hinton agar from wells where no detectable growth was detected. Results/Discussion: Only the hexane extract of the leaves demonstrated bacteriostatic effect against the strains \textit{R. ornithinolytica} and \textit{C. freundii} (MIC = 6400 μg/mL). According to previous studies, the essential oil of this species has shown to be effective against \textit{Aeromonas hydrophila} through \textit{in vitro} and \textit{in vivo} tests. Conclusion: The antibacterial activity verified for the hexane extract of \textit{H. ringens} leaves is relevant, considering that the strains tested are important pathogens of fish, as well as possible pathogens to humans.

Acknowledgements: The authors are grateful to CNPq, FAPERGS and CAPES for financial support.

IN VIVO TOXICITY EVALUATION OF STEROIDAL SAPONIN IN ZEBRAFISH (Danio rerio) EMBRYOS

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Introduction: Hecogenin acetate (HA) is a steroidal saponin that has anti-inflammatory, antinociceptive and antihyperalgesic activity already reported in the literature. However, there are no reports of toxicity studies. Therefore, the present study aimed to evaluate the toxicity of HA in zebrafish embryos. Methods: Toxicity assays were realized according to Guidelines for the Testing of Chemicals (OECD), number 236: Fish Embryo Acute Toxicity Test and conducted in 24-well plates with five embryos (4-32 cell stage) per treatment/concentration at 28 °C. Embryos were exposed to E2 medium (control) and HA different concentrations (5, 20, 40, 100 mg/kg). After, were monitored by fluorescence microscope during for 24, 48, 72 and 96 hours post-fertilization, for evaluation of malformation and mortality. This study was approved (number 1369/15) by the local animal welfare ethical committee (DEC) of Butantan Institute. Results and discussion: The results showed that HA was not present difference significant in survival of zebrafish embryos in concentrations of 5, 20, 40 and 100 mg/kg when compared to the E2 medium. The embryos hatched from 48-72h, considered the normal period and no malformation was observed. These results were positive, considering that zebrafish has been successfully used as a model organism to toxicity evaluation of therapeutic agents and chemicals, due to unique biological features of zebrafish such as robust resemblance of its genome to the human genome. Conclusion: In view of the above, we can conclude that HA does not present toxicity in concentrations of 5, 20, 40 and 100 mg/kg, thus suggesting therapeutic safety in these concentrations.

Financial support and acknowledgements: CAPES, CNPq, FINEP, FAPITEC/SE, REDE ZEBRAFISH OF THE IMMUNOREGULATION UNIT, SPECIAL LABORATORY OF APPLIED TOXINOLOGY (CEPID/FAPESP), BUTANTAN INSTITUTE OF SÃO PAULO.
STUDY OF THE CHEMICAL COMPOSITION OF PLANTS AND EXTRACTS OF MEDICINAL PLANTS, THROUGH X-RAY FLUORESCENCE TECHNIQUE

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Introduction: Plant extracts are mostly used in different types of products for segments in different areas, such as Pharmaceutical, Cosmetic, Food, and Veterinary, being employed in different dosages and applications. With this in mind, it is necessary to investigate the chemical composition of these extracts as a way to avoid the presence of contaminating elements harmful to health, above levels established by regulatory agencies, such as contamination by heavy metals Pb, As, Hg and Cd. Thus, the objective of this study is to evaluate the chemical composition of plants and plant extracts, through the technique of fluorescence X-rays by energy dispersion (EDXRF), evaluating not only the final chemical composition of the extracts, but also as production and purification process may interfere with the final product, from the standpoint of their chemical composition.

Methods: The extracts analyzed were obtained by the spray drying technique. For the fluorescence analyzes, tablets of the extracts and of the ground plants were made, using compression machine adjusted to the pressure of 15 T, producing tablets of 22 mm of diameter by 3 mm of height. The fluorescence system was calibrated using calibration pellets containing known amounts of the major elements of interest. Fifteen samples of plant extracts and five of plants were investigated. The qualitative and quantitative elemental analysis involved the investigation of the following elements: Ca, Cl, K, P, Si, As, Ba, Bi, Br, Cd, Co, Cr, Cu, Fe, Hg, Mn, Mo, Nb, Ni, Pb, Pd, Rh, Sc, Sn, Sr, Ti, U, V, W, Zn and Zr. The fluorescence system has a sensitivity to indicate the presence of chemical elements and their respective concentrations, from the element Aluminum to Fermion, with a concentration of parts per million (ppm). The quantification of the inorganic elements detected concentrations above the limit allowed for some heavy metals. The samples were analyzed in the Laboratory of Applied Nuclear Physics of Sorocaba University, Sorocaba, SP, Brazil (Lafinau).

Anti-Trypanosoma Cruzi AND CYTOTOXIC ACTIVITIES FROM Cattleya nobilior Rch.F. (Orchidaceae)

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Cattleya nobilior belongs to Orchidaceae family and this species is underexplored in relation to the chemical and biological properties. Phenantrene and stilbenoids derivatives have been described from species of Orchidaceae, which have received great interest because of their biological properties, especially anticancer. Our study aimed to determine the chemical composition from C. nobilior extracts (dichloromethane added methanol 95:5 and 1:1, v/v) of rhizomes by LC-DAD-MS extracts and to evaluate theirs anti-T. cruzi, cytotoxic (on Vero cells) and antitumoral activities (MCF-7 cells)LC-DAD-MS analysis allowed the identification of N-feruloyl tyramine, trans-methoxy-resveratrol, batatasin III, gigantol and phenantrene and stilbenoid derivatives. The IC50 on epimastigotes forms of T. cruzi was 82.9 µg/mL. The CC50 on Vero cells was 274.7 µg/mL while the CC50 on MCF-7 tumor cells was 10.1 µg/mL. This study demonstrates the antitumol and anti-T.cruzi potentials of the constituents from C. nobilior, showing that this species is a promising source of bioactive compounds and stimulates bioguided studies for determination of them.

Acknowledgments: CAPES, CNPq, Funedect.
INCLUSION COMPLEX CONTAINING NARINGENIN AND HYDROXYPROPYL-B-CYCLODEXTRIN PRODUCES ANTIHYPERALERGIC EFFECT IN A MICE LIKE-NEUROPATHIC PAIN MODEL

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Neuropathic pain (NP) results from disease conditions or trauma to the nerves. NP is caused by a lesion or disease of the somatosensory system, and affects 7–10% of the general population. Patients with NP experience spontaneous burning pain that radiates outside the area of innervation, exquisite sensitivity to light touch stimuli that are perceived as painful sensations (allodynia), and increased sensitivity to painful stimuli (hyperalgesia). The clinical treatment is inefficient creating a hiatus in the treatment currently used and taking suffering for patients. Natural products, such as flavonoids, have shown promise as a source of new chemical entities for NP, but some are not very solvable in waters, being necessary the use of pharmaceutical technologies like the cyclodextrins (CDs) seeking to improve these characteristics and its bioavailability has been employed. Thus, we aimed to enhance analgesic effect using an inclusion complex containing naringenin, a Citrus flavonoid, and hydroxypropyl-β-cyclodextrin (HPβCD) in mice like-NP model (sciatic nerve crush injury, SNCI). Sensory and motor parameters, hyperalgesic behavior and the sciatic functional index (SFI), respectively, were significantly improved (plevels of p75NTR ICD and p75NTR full length as well as phospho-JNK/totalJNK ratios were preserved by NA-HPβCD treatment. Together, we demonstrated that NA and NA-HPβCD enhanced the regeneration process, sensory response and motor function recovery in the SNCI-model in mice.

THE EFFECT OF SILYMARIN AND SILIBININ ON Helicobacter pylori GROWTH AND VIABILITY OF GASTRIC TUMORAL CELLS

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Introduction: Silymarin is a complex extract obtained from fruits and seeds of the Silybum marianum (L.) Gaertn, used to treat diseases related to the hepatic system, which silibinin is the main component. Although this extract is much studied little is known of its effects on gastrointestinal diseases caused by Helicobacter pylori infection. In this context, the present study aims to evaluate the anti-H. pylori and cytotoxic activities on the gastric adenocarcinoma of these substances. Methods: The anti-H. pylori activity was evaluated against ATCC 43504 and 43629 by determination of the Minimal Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC). The cytotoxicity in human gastric adenocarcinoma cells (ATCC CRL 1739) was performed by MTT. The results were expressed as percent of inhibition and concentration inhibitory 50% (IC₅₀). Results and discussion: The results in H. pylori ATCC 43504 showed MIC of 1024 μg/mL and 256 μg/mL for silymarin and silibinin, respectively, and MBC of 1024 only for silibinin, while for ATCC 43629 showed MIC of 512 and 256 μg/mL for silymarin and silibinin with no MBC for both substances at tested concentrations. The cytotoxic activity against adenocarcinoma cells after 48 and 72 hours presented IC₅₀ of 57.04 ± 5.12 μg/mL and 47.89 ± 3.40 μg/mL (silymarin) and 61.36 ± 5.48 μg/mL and 31.35 ± 5.39 μg/mL (silibinin), respectively. Conclusions: These results identify the biological efficacy of silymarin and silibinin against H. pylori and adenocarcinoma cells, suggesting the importance of further investigations to become an alternative for treatment of gastric disease.

Financial support and acknowledgements. UFES, CNPq and FAPES.
Introduction: Kalanchoe brasiliensis Cambess. (Crassulaceae DC.) is a native Brazilian plant popularly known as “saião” and traditionally used to treat anti-inflammatory and infectious processes. Based on these findings, this study evaluated the topical anti-inflammatory effect of the hydroethanolic extract at two different concentrations, 50% and 70%, obtained from K. brasiliensis leaves collected in January 2016 (HEJ50 and HEJ70).

Methods: Ear edema was induced in Swiss mice (n = 6) by topical application of phenol (10% v/v per ear) and capsaicin (200 µg/ear). HEJ50 and HEJ70 (0.10, 0.50 and 1.0 mg/ear) were applied 15 minutes after and 30 minutes before phenol- or capsaicin-induced mice ear edema, respectively. After 2 hours, the measurement of ear weight was determined. Dexamethasone (0.10 mg/20 µL acetone/ear) was used as positive control. The experimental protocol (number 005/2016) for the animal care and treatment was approved by the local Ethical Committee, which followed the recommendations of the Brazilian College of Animal Experimentation (COBEA).

Results and discussion: Topical application of HEJ50 and HEJ70 (0.10, 0.50 and 1.0 mg/ear) significantly inhibited the mass ear, as follows: phenol [HEJ50 (93.60, 93.09, and 95.01%) and HEJ70 (93.35, 94.24 and 95.65%); p < 0.001] and capsaicin [HEJ50 (59.42, 48.55 and 51.96%) and HEJ70 (49.68, 45.01, 62.96%); p < 0.001]. Dexamethasone was effective in inhibiting ear edema.

Conclusions: These results support the traditional use of K. brasiliensis to treat anti-inflammatory processes and demonstrate its potential as a promising source of active compounds for the development of remedies to treat dermatitis disorders.

Acknowledgements: This study was supported by Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG Grant n° CDS-APQ-04680-10), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Programa de Alianças para a Educação e a Capacitação (PAEC)-Organização dos Estados Americanos (OEA)/Grupo Coimbra de Universidades Brasileiras (GCUB), and Pró-Reitoria de Pós-Graduação e Pesquisa da Universidade Federal de Juiz de Fora.

Tithonia diversifolia (ASTERACEAE) ETHANOLIC LEAVES EXTRACT INHIBITHIS FUNCTIONS RELATED TO NEUTROPHIL CHEMOTAXIS

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Introduction: T. diversifolia has been used in the traditional medicine in several countries as anti-inflammatory and against other illnesses. In this context, we investigated the in vivo and in vitro effects of T. diversifolia ethanolic extract obtained from leaves on neutrophil trafficking from the blood into an inflamed tissue and on cell-derived secretion of chemical mediators. Methods: Anti-inflammatory activity was investigated using carrageenan-induced inflammation in the subcutaneous tissue of male Swiss mice orally treated with the T. diversifolia extract (10, 30 or 100 mg/kg). The leukocyte influx (optical microscopy), secretion of chemical mediators (TNF and IL-1, enzyme-linked immunosorbent assay) and protein exudation (Bradford reaction) were quantified in the inflamed exudate. Histological analysis of the pouches was performed. Lipopolysaccharide-induced adhesion molecule expression (CD62L and CD18, flow cytometry) was in vitro quantified using oyster glycogen recruited peritoneal neutrophils previously treated with the extract (1, 10, or 30 µg/mL). Results and discussion: T. diversifolia extract oral treatment promote a dose-dependent reduction in the neutrophil migration as well as decreased in total protein, IL-6 and TNF-α levels in the inflamed exudate. In vitro treatment with T. diversifolia shedding of β2 integrin expressions, without alter CD62L expression. Conclusions: Together, the results herein presented show that T. diversifolia extract displays important in vivo and in vitro anti-inflammatory actions by blocking pathways of neutrophil migration and secretion, suggesting its therapeutic application to acute inflammatory reactions.

The UNIVALI Animal Research Ethics Committee approved all experimental procedures (034/17).
ASSESSMENT OF ANTIPROLIFERATIVE ACTIVITY OF Annona ambotay (AUBL.)

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The discovery of new natural compounds for the development of innovative therapeutic approaches is arising interest in the pharmaceutical industry. Due to the scarcity of data on the biological activities of the Annona ambotay (Aubl.), the objective of the present study was to evaluate the in vitro toxic activities using the dry extract from A. ambotay barks. The cell cytotoxicity (L929, MDA-MB-231 and MCF7) was evaluated by the MTT assay, and the lethality assay on Artemia salina was also performed.

The results for toxicity in murine fibroblasts (L929) indicate a reduction in cell viability from 43% to 84% at the concentrations tested, when compared to control group. The results of cytotoxicity in breast cancer tumor cells evidenced an antiproliferative effect, with greater reduction of viability at the highest concentrations for both cell lines tested, with IC_{50} of 116.32 μg mL^{-1} for MDA-MB-231 and IC_{50} of 126.87 μg mL^{-1} for MCF7. A toxic effect was also evidenced in the Artemia salina assay, with a CL_{50} of 296.78 μg mL^{-1}. According to the results obtained in the study, the extract presented promising anticancer activity against breast cancer cell lines associated to toxic effect in the Artemia salina assay.

IDENTIFICATION OF CHALCONES FROM Varronia dardani (TARODA) J.S. MILL (BORAGINACEAE) AND EVALUATION OF THEIR POTENTIAL INHIBITION OF BIOFILM FORMATION

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Introduction: Varronia dardani is a well distributed species among the Brazilian Northeast states and Caatinga biome. Objectives: To contribute to the chemical knowledge of the genus, through phytochemical study of V. dardani leaves, with a subsequent study of Minimum Inhibitory Concentration (MIC) and Inhibition of Biofilm Formation (IBF). Methods: The crude ethanolic extract of V. dardani leaves was partitioned and the dichloromethane phase (DP) was used to perform a medium pressure liquid chromatography. The compounds structures were determined by Nuclear Magnetic Resonance (1H and 13C) and Electrospray Ionization Mass Spectrometry. Enterococcus faecalis and Streptococcus salivarius were used to MIC evaluation, by broth microdilution. The MIC served as a reference for the IBF assay. Results: The DP chromatographic fractionation resulted in the isolation of pinostrobin chalcone (Vd-1) and the identification of its mixture with gymnogrammene (Vd-2), this is the first time these substances have been reported in the species. For S. salivarius, the MIC was 250 μg/mL for the isolated compound and 500 μg/mL for the mixture; in contrast for E. faecalis, the mixture showed MIC of 500 μg/mL. With regard to IBF test, the lowest concentration of the compound isolated and the mixture that showed a strong inhibition against E. faecalis was 1000 μg/mL; to S. salivarius, the results were 250 μg/mL for Vd-1, and 1000 μg/mL for the mixture. Conclusions: The phytochemical study of V. dardani led to the isolation and identification of two chalcones. Pinostrobin chalcone is antimicrobial and antibiofilm at concentrations greater than 250 μg/mL.
OPTIMIZATION OF THE IRIDOID SPECIOSIDE BIOTRANSFORMATION BY Aspergillus niger.

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Tabebuia aurea has been used in traditional medicine for treatment of stomach problems, and the iridoid specioside was found in higher concentration in this species. Literature supports that the fungi of the genus Aspergillus could successfully biotransform specioside. Thus, the aim of this study was the optimization of the process of specioside biotransformation by A. niger and the evaluation of the products that could be formed during the biotransformation process. The biotransformation assay was started with incubation of A. niger’s spore in the liquid culture medium. After 48 hours, 50 mg specioside was added to the culture medium, an aliquot of medium were monitored every 2 hours through thin layer chromatography and HPLC-DAD-MS. The specioside was wholly biotransformed in 52 hours, after 40 hours of inoculation of specioside, the chromatogram confirmed the formation of a new compound with a molecular formula of C₁₈H₁₈O₇, which correspond to specioside in non-glucose form and, at 44 hours the coumaric acid (C₉H₈O₃) was also detected. It was possible to observe during the 52h of biotransformation that the formation of the non-glycosylated species was proportional to the consumption of the glycosylated specioside, these data can be supported by a decay curve of the starting material. The process has proved to be efficient in the selective elimination of the sugar from the specioside and the time is a crucial point to maximize the yield of the reaction. Also, the biosynthesized compound was not previously described in the literature.

COMPARATIVE ANALYSIS ABOUT THE CHEMICAL COMPOSITION OF EXTRACTS OF Mentha x villosa Hudson BY GC-MS, OBTAINED WITH THREE DIFFERENT EXTRACTIVE TECHNIQUES

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Introduction: Mentha x villosa H. belongs to Lamiaceae family, popularly known as “hortelã-da-folha-miúda”. In Brazilian Northeast it is used for diarrhea and stomach cramps. An important factor in extract obtainment is the choice of the proper extractive technique, since it can influence the yield of the secondary metabolites in extract. Objective: To perform a comparison of the content of the secondary metabolites from the extracts of Mentha x villosa using different extractive techniques. Methods: The aerial parts were collected in the garden of the Drugs and Medicines Research Institute of the Federal University of Paraíba. Thus, 8g of plant material were ground in a multiprocessor and submitted to extractive processes of static maceration, dynamics and ultrasound for 2 hours. Results: It was possible to identify 9 compounds in the three extraction processes with yield above 0.1%. The major chemical constituent was rotundifolone with a percentage content of 82.0% for dynamic maceration, 88.29% for static maceration and 80.47% for ultrasonic extraction. The second highest yielding compound was carvone with 0.99% and 6.45% for the static maceration and ultrasound, respectively. Conclusion: The chemical characterization of the extracts showed that rotundifolone was the major constituent with yields over than 80%. The ultrasound extraction technique presented the best area percentage of the identified constituents, being the extractive method of choice to obtain a good yield of the constituents. This study confirmed rotundifolone as marker and contributed with the chemotaxonomic knowledge of the genus and species studied. Financial Support: CNPq.
HECOGENIN ACETATE/B-CYCLODEXTRIN: INFLUENCE OF INCLUSION COMPLEX FORMATION ON THE MORPHOLOGY AND DISSOLUTION PROFILE OF HECOGENIN ACETATE

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Hecogenin acetate (HA) belongs to the class of steroidal glycosides that many years has been used in the pharmaceutical industry as a precursor in the production of corticosteroids. However, HA has an amphiphilic characteristic, which may hamper its solubility in aqueous medium and consequently its bioavailability when administered orally. Therefore, the present study aimed to evaluate the influence of inclusion complex (IC) formation on the morphology and dissolution profile of HA. IC was obtained by freeze-drying method, as described in the literature. Subsequently, the IC was analyzed by electrospray ionisation mass spectrometry (ESI-MS), X-ray diffractometry (XRD) and laser diffraction (LD). Then, was evaluated the dissolution profile of HA alone and IC. ESI-MS analysis were performed on a Bruker mass spectrometer. The conditions used were: nebulizing gas pressure, 10 psi (N2); drying gas flow 4.0 L/min at 210 °C; capillary voltage +4500kV and range from m/z 100 to 2200. XRD patterns were obtained on a Siemens D5000 X-ray diffractometer equipped with tube of Cu K-alpha, in the interval of 3-35 °?. Laser diffraction analysis was performed using Mastersizer® 2000 and volume-weighted mean diameter (dV,50) was determined using the mie theory; and the polydispersity (span) was calculated using the values of diameters at 10 (dV,10), 50 (dV,50) and 90% (dV,90). Finally, the dissolution profile was performed in triplicate using dissolution test equipment, employing the apparatus paddle at 50 rpm in a dissolution medium of water with 0,5% sodium lauryl sulfate at 37 ± 0,5 °C. ESI-MS results showed the presence of HA in IC at m/z 1604,05. XRD results was possible to observe that HA and βCD have crystalline characteristic, different from the IC, that shows tendency to amorphization. This results corroborate with the LD, that presented homogenous distribution volume and decrease of IC particle size (dV,50 = 23,62 µm), when compared to HA alone (dV,50 = 289,88 µm) and βCD (dV,50 = 239,30 µm). The amorphous characteristic and the particle size of the IC verified in the XRD and LD respectively, had a positive influence on the dissolution profile of the HA. In 60 min accordance with the results, more than 80% of HA/βCD was delivered, against less than 40% compared with HA alone. In view of the above, we can suggest that inclusion complex formation reduce particle size, increase the solubility and possibly bioavailability of amphiphilic compound when administered orally.

PHENOLIC SUBSTANCES ISOLATED FROM Ludwigia octovalvis L. (ONAGRACEAE) AND EVALUATION OF ANTIODXIDANT ACTIVITY OF IT’S EXTRACT

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Introduction: Ludwigia octovalvis (LO) species is used on popular medicine against some diseases, such: hypertension, diabetes, etc. The aim of the study was to isolate and identify compounds from LO and evaluate the antioxidant activity of its extract.

Methods: The whole plant was macerated with ethanol (95%). 55.13 g of the Crude Ethanolic Extract (CEE) was partitioned and yielded 3.5 g of the acetate phase. After this procedure, 3.0 g of the acetate phase was applied to medium pressure liquid chromatography, allowing the isolation of LO1 (12 mg) and LO2 (4 mg). The substances were identified by ¹H and ¹³C NMR spectroscopy, the substance LO1 presented 15 signals of carbon atoms, leading to the proposition that the substance was a flavonoid. The ¹H NMR data strengthened this proposal, presenting ring B couplings with ABX system. In the ¹H NMR spectrum, the substance LO2 showed a singlet in δH 7.46. ESI-MS (negative mode) demonstrated the ion of the deprotonated molecule in m/z 301.02. This peak was selected and second order analysis (MS²) was performed and it was identified as a phenolic acid. The CEE of LO presented an EC50 of 44.27 ± 0.20, indicating good antioxidant activity when compared with ascorbic acid (EC50 10.88 ± 0.05). The antioxidant effect was attributed to the high content of phenolic substances present in the extract, according to the results obtained on total phenolic content (203.56 ± 0.08 mg EAG/mg de extract).

Conclusions: The study allowed the identification of 3,5,7,3’,4’-pentahydroxyflavone (LO1) and ellagic acid (LO2). The extract presented high antioxidant potential.

Acknowledgements: CAPES and CNPq.
ID: 174

NOVEL TERPENOIDS FROM Stillingia loranthaceae: SEARCH FOR METABOLITES RELATED BY LC-ESI-MS2-MN

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Introduction: The genus Stillingia (Euphorbiaceae) has approximately thirty species. In Brazil are found seven of them, four pre-dominate in Caatinga. Some macrocyclic diterpenes present in this vegetal group showed cytotoxicity activity against cancer cell lines of human kidney and lung. The study of other diterpenes and its biological activity have been stimulating pharmacological and phytochemical investigations of Stillingia. Many species in this genus has its chemical composition unknown, among them the species S. loranthaceae, endemic of Caatinga. Thus, this work describes new terpenoids obtained from root barks. Method: The plant material was collected in Morro do Chapéu-BA, the voucher was deposited in the herbarium of UFBA. It was macerated in hexane and fractionated in HPLC-Prep, posteriorly analyzed by LC-ESI-MS²-MNN. Results and discussion: From it was possible to isolate two novel 28-nor-Triterpenes: 3β-benzoyl-28-noroleanane-14-en-16-one-23-oic acid (1), and 3β-cinnamoyl-28-noroleanane-14-en-16-one-23-oic acid (2), four new tigliane diterpenes 12-deoxyphorbol-13-(5Z)-tetradecanoate (3), 12-deoxyphorboldehydye-13-(5Z)-tetradecanoate (4), 12-deoxyphorboldehydye-13-dodecanoate (5) and 12-O-hexadecanoate-4α-deoxyphorbol-13-acetate (6), three known 12-deoxyphorbol-13-dodecanoate (7), 12-deoxyphorbol-13-tetradecanoate (8), 12-O-hexadecanoate-4α-deoxyphorbol-13-acetate (9), and three flexibilene diterpenes: tonantzitlolone A (10), tonantzitlolone B (11) and tonantzitlolone C (12). The study performed in LC-ESI-MS², associated to the analysis by Molecular Networking (MN) and its fragmentation patterns allowed observing the presence of seven putative structures of others 28-nor-Triterpenes not described yet in literature. Conclusion: This work describes the occurrence of new terpenoids and proposes the presence of other new 28-nor-Triterpenes in root barks of Stillingia loranthaceae.

ID: 188

METHANOLIC EXTRACT OF Garcinia achachairu RUSBY (CLUSIACEAE) LEAVES INHIBITS NEUTROPHIL INFUX AND CYTOKINE SECRETION

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Introduction: Garcinia achachairu is popularly used because of its healing effect, digestive properties and to treat inflammatory processes in general. We investigated the in vivo and in vitro effects of G. achachairu methanolic extract obtained from leaves on neutrophil trafficking from the blood into an inflamed tissue and on secretion of chemical mediators. Methods: Anti-inflammatory activity was investigated using carrageenan-induced inflammation in the subcutaneous tissue of male Swiss mice (six animals per group) orally treated with the G. achachairu extract (0.1, 1.0, 10 or 30 mg/kg). The leucocyte influx (optical microscopy), secretion of chemical mediators (TNF and IL-1, enzyme-linked immunosorbent assay) and protein exudation (Bradykin reaction) were quantified in the inflamed exudate. Histological analysis of the pouches was performed. Lipopolysaccharide-induced adhesion molecule expression (CD62L and CD18, flow cytometry) was in vitro quantified using oyster glycogen recruited peritoneal neutrophils previous treated with the extract (1, 10, or 100 µg/mL). Results and discussion: G. achachairu extract oral treatment caused a dose-dependent reduction in the neutrophil migration, IL-1 and TNF-α levels in the inflamed exudate, especially at the dose of 30 mg/kg, but did not alter the total protein levels. In vitro treatment with G. achachairu shedding of L-selectin and β2 integrin expressions (dose of 30 mg/kg). Conclusions: The results herein presented show that G. achachairu extract displays important in vivo and in vitro anti-inflammatory actions by blocking pathways of neutrophil migration and secretion, suggesting its therapeutic application to acute inflammatory reactions. The UNIVALI Animal Research Ethics Committee approved all experimental procedures (061/17).
**ID: 192**

**ANTIFUNGAL EFFECT OF EUGENOL DERIVATIVES AGAINST Candida albicans AND CYTOTOXICITY EVALUATION ON MACROPHAGES LINEAGE**

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**Introduction:** Eugenol, a natural compound obtained from clove (*Syzygium aromaticum* L.) with known antifungal activity on *Candida albicans*, which is one of the main causes of morbidity and mortality. Since its oral treatment is associated with hepatic insufficiency, the development of new eugenol-inspired derivatives is a valuable strategy in the search of new active compounds with less cytotoxic effect. In this context, the present study aims to evaluate the antifungal effect on *C. albicans* and cytotoxic activity on macrophage lineage of these compounds. **Methods:** Eugenol-derivatives were synthesized by Huisgen 1,3-dipolar cycloaddition. The synthesized compounds 2-[2-ethyl-4-(prop-2-en-1-yl)phenoxyl]acetonitrile (1); 2-chloro-3-[2-methoxy-4-(prop-2-en-1-yl)phenoxyl]-1,4-dihydropthalene-1,4-dione (2); 1-[[5-benzensulfonyl)methyl][phenyl]methoxy]-2-methoxy-4-(prop-2-en-1-yl) benzene (3); 4-(2,3-dibromopropyl)-2-methoxyphenol (4) and 5-[4-(cyanomethoxy)-3-methoxyphenyl]-4-Iodopentanenitrile (5) were purified by column chromatography using a hexane/ethyl acetate mixture (10:1). Antifungal effect on *Candida albicans* (ATCC 14053) was determined by Minimal Inhibitory Concentration (MIC) and Minimum Fungicide Concentration (MFC). Cytotoxicity was evaluated in vitro on macrophage lineage (ATCC 264.7 TIB-71) using the MTT assay and half the maximal inhibitory concentration (IC₅₀) was determined by linear regression analysis. **Results and discussion:** Eugenol, showed MIC and MFC of 400µg/mL. Semi-synthetic derivatives, named herein, 1, 2, 3, 4 and 5 showed MICs of 50µg/mL, 100µg/mL, 400µg/mL and 400µg/mL respectively, and MFC of 50µg/mL, 100µg/mL and 400µg/mL, respectively. MIC and MFC were not obtained for derivates 4 and 5. Cytotoxic activity (IC₅₀) of eugenol and its derivatives were respectively 91.03µg/mL, 46.80µg/mL, 18.26µg/mL, 69.97µg/mL, 21.85µg/mL, 194.3µg/mL. **Conclusions:** The presented findings are a preliminary screening of a series of eugenol derivatives, and these initial results indicate the potential of such modifications in the development of active compounds against *C. albicans*. **Financial support:** FAPES and UFES.

**ID: 200**

**Spondias mombin L. REDUCES CUTANEOUS INFLAMMATION IN MICE**

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**Introduction:** Spondias mombin L. is a fruitful species used for the treatment of vomiting, diarrhea, dysentery, hemorrhoids, wounds and inflammation. In this study, the topical anti-inflammatory effect of extracts from S. mombi was evaluated. **Methods:** EEBSM (barks) and EEWSM (wood) extracts were obtained by static maceration in ethanol. These extracts were analyzed by HPLC-DAD-UV using chemical markers. The anti-inflammatory activity of the extracts was evaluated using the ear edema model induced by Croton oil application in Swiss mice (n = 8) (protocol number 001/2017 approved by the Ethical Committee for Handling / UFJF). The treatments were performed with 0.1, 0.5 and 1.0 mg extract / ear. Measurements of edema thickness (µm) were evaluated at 6 and 24 hours post application. Following the euthanasia of the animals, the mass (mg) of the edema was measured. Fragments were collected for histopathological analysis and dosage of inflammatory markers (myeloperoxidase - MPO and N-acetyl-β-D-glucosaminidase -NAG). **Results and Discussion:** Ellagic acid was identified in the samples. The treatment with ECSM and EEMSM at doses of 0.1, 0.5 and 1.0 mg / ear inhibited edema thickness in 53.83%, 58.27%, 63.06%, 37.51%, 39. 48%, 52. 23% within 6 hours of application, respectively. After 24 hours the reduction was 56.22%, 61.18%, 58.01%, 45.58%, 51.93% and 63.67% (p<0.05). **Conclusions:** The results suggest that EECSM and EEMSM have topical anti-inflammatory activity, which supports the traditional use of S. mombin. **Financial Support and acknowledgements:** CAPES, FAPEMIG, CNPq and UFJF.
CYTOTOXICITY, ANTIFUNGAL AND ANTIOXIDANT ACTIVITIES OF Piper aduncum L.

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Background: Candidiasis is the yeast infection with the highest incidence in the overall population. This disease can be acquired through contact with fungus with the ability to form yeast, most commonly yeast from the genus Candida, including Candida albicans and non-albicans species. The numbers of cases are increasing concurrently with the number of species resistant to available antifungal treatments, which makes drug treatment of this pathology difficult. Against this obstacle, natural products can contribute to the development of effective antifungal drugs with low toxicity, making the study of the biological activity of native plants attractive. The aim of this study was to perform a phytochemistry screening and to evaluate the antifungal and antioxidant potential and toxicity of dry extract from Piper aduncum L. Methods: The extract of the leaves was subjected to phytochemistry screening, antifungal assays against strains identified as Candida albicans ATCC 10231, C. glabrata CCT 0728, C. krusei CCT 1517, and C. guilliermondii CCT 1890. Antioxidant potential was evaluated by using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method and toxicity by bioassay with Artemia salina Leach. Results and discussion: The presence of flavonoids, cumarins, tanins, and terpenes in the dry extract was identified. A fungistatic property was shown against all strains, with values of MIC ranging from 19.53 µg mL⁻¹ to 156.25 µg mL⁻¹ and MFC > 5.000 µg mL⁻¹. P. aduncum demonstrated an IC₅₀ of 3.76 ± 0.16 µg mL⁻¹, indicating high antioxidant potential, and the extract was non toxic for Artemia salina Leach, with a LC₅₀ of 1,148.14 µg mL⁻¹. Conclusion: The results obtained in this study confirm the importance of P. aduncum as a source of substances with biological activity.

EVALUATION OF THE EFFECTS OF Maytenus ilicifolia MART. EX REISS (CELASTRACEAE) EXTRACTS IN THE CYP3A ACTIVITY

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Introduction: The leaves of Maytenus ilicifolia Mart. Ex Reiss (Espinheira-Santa) are widely utilized in popular medicine for ulcer and gastritis treatment. Despite of the absence of adverse effects related with its consumption, there is a lack of information regarding possible interactions when coadmininistrated with conventional drugs. Therefore, the aim of this study was to evaluate the effects of M. ilicifolia extracts on CYP3A activity. Methods: M. ilicifolia extracts were obtained by infusion (I) and turbo-extraction (T70). The pharmacokinetic profile of midazolam 20 mg·kg⁻¹ (CYP3A substrate) following its oral coadministration with each extract (10 mg·kg⁻¹) in male Wistar rats (n=8) was evaluated and compared with that from a control group. This study was approved by UFSJ animal research ethics committee (protocol 004/2016). Results and discussion: The I and T70 extracts promoted a significant increase in midazolam ASC₁₆₄₀(I = 1947 ± 667.8 ng·mL⁻¹·h⁻¹; T70 = 2076 ± 372.5 ng·mL⁻¹·h⁻¹) and Cₘₚₙ(I = 1770 ± 764.5 ng·mL⁻¹; T70 = 2134 ± 418.2 ng·mL⁻¹) in comparison with the control group (ASC₁₆₄₀: 662,3 ± 316,0 ng·mL⁻¹·h⁻¹; Cₘₚₙ: 424,0 ± 90,45 ng·mL⁻¹). Those changes were accompanied by a CI/F reduction (I = 11,05 ± 3,65 L·kg⁻¹·h⁻¹; T70 = 9,08 ± 1,21 L·kg⁻¹·h⁻¹ versus Control = 32,31 ± 12,48 L·kg⁻¹·h⁻¹, respectively) and were attributed to the inhibition of CYP3A midazolam metabolism. Conclusions: Coadministration of M. ilicifolia extracts with drugs metabolized by CYP3A may not be free of toxicity and should be done with caution. Future studies are needed to assess the clinical relevance of this interaction. Acknowledgments: Fapemig for financial support grant APQ -02155-16; UFSJ for fellowship support.
TOPICAL ANTI-INFLAMMATORY ACTIVITY OF THE EXTRACT AND ISOLATED COMPOUND FROM Centaurea benedicta L.

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Introduction: Centaurea benedicta, popularly known as “cardo-santo”, is a plant used in traditional medicine as tonic, antidepressant, anti-inflammatory, antibacterial and antiseptic. The present study evaluated the topical anti-inflammatory activity of the extract and cnicin from C. benedicta in animal model. Methods: Fresh leaves were subjected to foliar washing in dichloromethane:ethanol (9:1) to acquire the extract DEECB. Ear edema was induced by Croton oil in Swiss mice and treated with doses of 0.1, 0.5 and 1.0 mg/ear of DEECB or cnicin (protocol number 022/2018 was approved by the Ethical Committee for Handling/UFJF). Analysis of variance followed by Tukey’s test was used to measure the significance level for $p < 0.05$. Results and discussion: After 6 h of treatment, DEECB reduced the edema thickness in 60.67, 60.73 and 60.40% at the doses of 0.1, 0.5 and 1 mg/ear, respectively, while cnicin decreased in 51.29, 69.71 and 72.90% in these doses. DEECB (59.76, 76.07 and 82.22%) and cnicin (39.59, 56.00 and 69.79%) also inhibited the edema thickness at the doses of 0.1, 0.5 and 1mg/ear after 24 hours of treatment. In addition, at the doses of 0.1, 0.5 and 1 mg/ear, DEECB reduced the weight in 68.07 (0.1 mg/ear), 76.60 (0.5 mg/ear) and 78.60% (1 mg/ear), while cnicin decreased in 89.64 (0.1 mg/ear), 94.32 (0.5 mg/ear) and 94.72% (1 mg/ear). Conclusions: The results suggest that DEECB and cnicin from C. benedicta present topical anti-inflammatory activity, which open up new possibilities for the treatment of disorders associated with cutaneous damage.

Financial support and acknowledgements: CAPES, FAPEMIG, CNPq and UFJF.

CHEMICAL PROFILE, PHENOLIC COMPOUNDS AND IN VITRO ANTIOXIDANT ACTIVITY OF Bambusa vulgaris

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Introduction: Natural products are a great source of new drugs, since they have many compounds that act as antioxidant. Bambusa vulgaris is a plant used in Brazil to treat inflammatory disorders, which has oxidant participation, so the aim is to evaluate chemical profile and antioxidant activity of B. vulgaris. Methods: Leaves was collected, dried and ground and extracted with methanol using Soxhlet apparatus, the extract was evaporated and the chemical profile was performed using Thin Layer Chromatography (TLC) according to Wagner and Bladt (2012), and to determine phenolic content Folin-Ciocalteu’s method was performed. Antioxidant activity was evaluated by ABTS, FRAP and DPPH. The results from phenolic contents were expressed in Pyrogallol Equivalent/100g of plant material and the antioxidant activities were expressed as IC50=µg/mL Results and discussion: The TLC evaluation demonstrated the presence of flavonoids and coumarins, also, chemical phenolic content was 564mg/100g of plant material. Antioxidant activity was great for FRAP (20.91µg/mL), moderate for ABTS (89.06µg/mL) and weak for DPPH (228.65µg/mL), observed by increase on IC50 values. Conclusions: The results show that B. vulgaris has antioxidant activity, and a low content of total phenolic compounds, also more studies needs to be conducted to determine the biological effects of B. vulgaris.
CHANGES IN THE CHEMICAL PROFILE AND SKIN PENETRATION OF BIOTRANSFORMED GREEN COFFEE EXTRACTS

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Introduction: Green coffee beans (Coffea arabica L.) contain a complex blend of phenolic compounds with antioxidant activity. In this study, the green coffee fermentation was carried out by Aspergillus oryzae aiming the biotransformation of the phenolic compounds into lower molecular mass molecules targeting a greater skin penetration.

Methods: The antioxidant activity of the hydroethanolic extracts of non-biotransformed and biotransformed coffee for 24, 36 and 48 hours was evaluated by the 2,2-diphenyl-1-picryl-hydrazyl (DPPH·) spectrophotometric and thin layer chromatography (TLC) methods. Chlorogenic acid, caffeine and caffeic acid quantification was carried out using high-performance liquid chromatography (HPLC). The chemical characterization of extracts was performed using the ultra-high-performance liquid chromatography coupled to mass spectrometry with time-of-flight analyzer (UPLC-MS-Q-TOF). Penetration studies were conducted on Franz diffusion cells (pig ear skin) and the quantification was performed using HPLC.

Results and discussion: HPLC, TLC and UPLC-MS-Q-TOF analyzes showed chemical changes in green coffee. It was evidenced the breakage of the esters of chlorogenic acids with formation of quinic and caffeic acids after 36 hours of solid state fermentation without loss of the antioxidant activity. The in vitro penetration results showed that caffeine was the only compound able to go through the skin. Caffeine penetration was higher when the formulation added by the biotransformed extract was used.

Conclusions: Biotransformation of green coffee has shown to be an effective strategy to promote changes in the profile of its secondary metabolites. Additionally, results reinforce the importance of skin penetration studies to guarantee the efficacy of pharmaceutical and cosmetic formulations.

Financial Support: This study was supported by Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG Grant nº CDS-APQ-00949-14), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq Grant nº 456366/2014-8), and Pró-Reitoria de Pós-Graduação e Pesquisa da Universidade Federal de Juiz de Fora.

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EVALUATION OF THE EFFECTS OF Passiflora alata, Piper Methysticum AND Valeriana officinalis EXTRACTS IN THE ACTIVITY OF P-GLYCOPROTEIN

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Introduction: Passiflora alata, Piper Methysticum and Valeriana officinalis are widely used to treat anxiety. Although there is no evidence about the toxicity of those plants, possible herbal-drug interactions following their coadministration with conventional drugs still need to be unveiled. Therefore, the aim of this study was to evaluate the effect of Passiflora alata, Piper Methysticum and Valeriana officinalis extracts in the activity of P-glycoprotein (P-gp).

Methods: Buffer solution (pH 7.4) was used to solubilize the dried extracts of Passiflora alata (600 µg/mL), Piper Methysticum (150 µg/mL), and Valeriana officinalis (430 µg/mL). Caco-2 cells were cultured for 21 days and incubated with fexofenadine (FEX) 50 µM (P-gp substrate) in the absence or presence of each extract. Tariquidar (TAR) 3 µM was used as positive control. The cells were lysed with NaOH 1 M and neutralized with HCl 1 M. The intracellular concentration of FEX was determined by HPLC. The uptake was expressed as ng of FEX per mg of protein.

Results and discussion: The uptake of FEX by the cells treated with Piper methysticum was 2.8-fold higher than that from the negative control (18.9 ng/mg versus 6.6 ng/mg, respectively). The uptake after incubating the cells with TAR was 17.1 ng/mg. Passiflora alata and Valeriana officinalis did not affect the uptake of FEX by Caco-2 cells. Conclusion: This study suggests that coadministration Piper methysticum extracts may affect the disposition of drugs substrate of P-gp and may require dose adjustment to prevent adverse effects particularly in case of drugs with low therapeutic index.
CHEMICAL PROFILE, PHENOLIC COMPOUNDS AND IN VITRO ANTIOXIDANT CAPACITY OF Leonotis nepetifolia

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Introduction: Plants have a great source of antioxidant compounds, also, most of diseases has an oxidant pathogenesis involved, so they can be a source of new drugs. Leonotis nepetifolia is a plant used in Brazil to treat many diseases so, the aim of present study was to determine chemical profile and phenolic compounds and in vitro antioxidant capacity of L. nepetifolia leaves and inflorescence.

Methods: Plant material (inflorescences and leaves) was collected and extracted using Ethanol 70% (100g:400mL). The extracts were evaporated, freeze-dried and keep frozen until use. The phytochemistry screening was performed according to Wagner e Bladt (1996) and Phenolic and Tannins by Krepsy et al (2012). To determine the antioxidant activities ABTS, DPPH and FRAP tests were performed.

Results and discussion: Phytochemistry characterization demonstrated the presence of flavonoids, terpenes and coumarins for both extracts, Inflorescences (LNI) and Leaves (LNL). Total phenolic content was 4.256±0.221/100g and 4.863±0.292/100g, for LNI and LNL respectively, tannins content was 1.497±0.192/100g and 0.623±0.555/100g, for LNI and LNL. All the extracts show antioxidant activity, IC50 for ABTS (LNI: 48.63 and LNL: 72.18µg/mL), DPPH (LNI: 51.04 and LNL: 59.33µg/mL) and FRAP (LNI: 24.75 and LNL: 35.4µg/mL) methods. Conclusions: The results show that both extracts have a good antioxidant activity and chemical characterization demonstrated presence of phenolic and tannins, also presence of coumarin and other compounds, though more studies have to be conducted to determine the biological effects of L. nepetifolia.

BROWN PROPOLIS COMPOUNDS ABLE KILLING STAPHYLOCOCCUS AUREUS BIOFILM AND Trichomonas vaginalis

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Propolis is a resin produced by bees, with numerous biological activities. Its composition changes because its related to the flora of each region visited by bees and the queen genetic diversity. Ethanolic extracts and fractions, yielded by innovative accelerated solvent extraction methodology, were obtained from different samples of Brazilian brown propolis. They were assayed for antimicrobial, antibiofilm, anti-Trichomonas vaginalis, antioxidant capacity and total phenolic content. The chemical profile was obtained by LC-DAD-MS and eighty six compounds were identified from three propolis samples, including phenylpropanoic acids, flavonoids, chlorogenic acids, and prenylated phenylpropanoic acids. At concentration 125 μg/mL, propolis-fraction exhibited a reduction of 93% of Staphylococcus aureus in biofilm and reduced 100% of T. vaginalis viability with MIC at 400 μg/mL. The antioxidant capacity showed IC50 ranged from 2.32-3.80 μg/mL and the total phenolic content ranged from 38.82 to 151.42 mg/g of GAE/g. The artepillin C and others prenylated coumaric acid derivatives correlated positively activities against anti-biofilm, anti-T. vaginalis as well as with the antioxidant capacity and total phenolic content.

Acknowledgments: CAPES, CNPq, Programa de Pós-Graduação em Farmácia (UFMS).
ORAL ANTI-INFLAMMATORY ACTIVITY OF DICHLOROMETHANE FRACTION OF Siparuna guianensis Aublet LEAVES IN LPS-INDUCED PERITONITIS MODEL

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Introduction: Siparuna guianensis Aublet. (Siparunaceae) is popularly known as “negramina” and “capitú” in Brazil¹. Its leaves have been extensively used in folk medicine to treat diseases as rheumatism, inflammation³⁴ and body aches⁵⁶. In order to investigate S. guianensis leaves anti-inflammatory potential, in the present study it was induced a peritonitis model in mice with lipopolysaccharide (LPS). Method: Mice were randomly divided into groups (n=6) and were orally administered: Dichloromethane fraction of S. guianensis leaves (DF) (50mg/kg and 100mg/kg), dexamethasone (1mg/kg) as positive control and vehicle. One hour after treatment, 200 μL of LPS (25μg/mL) or saline solution 0.9% was injected intraperitoneally. Animals were euthanized 4 hours later and their peritoneal cavity were washed with 4mL of sterile phosphate buffered. The peritoneal fluid were collected and the number of leukocytes were determined. (Protocol #042/2015, CEEA-UFJF). Statistics: ANOVA followed by Tukey test. Results and Discussion: DF 100mg/kg and dexamethasone were able to significantly reduce the total number of leukocyte in 53% and 32%, respectively. It can be inferred that the DC contains substances that inactivate the LPS intrinsic signaling pathways, avoiding the expression of inflammatory cytokines, chemokines, growth factors and expression of adhesion molecules⁹, decreasing the recruitment of polymorphonuclear leukocytes on site⁹. Quercetin, kaempferol¹⁰ and lucenin¹¹ are flavonoids with reported anti-inflammatory activity and that were identified in S. guianensis, suggesting that these substances can be related to the activity found. Conclusions: These findings strongly suggest that DF is endowed with natural compounds with anti-inflammatory potential, encouraging further phytochemical studies.

Financial support: FAPEMIG, UFJF, CAPES, CNPq.

TOPICAL TOXICITY EVALUATION OF THE HEXANE FRACTION FROM PERESKIA ACULEATA MILLER (CACTACEAE) LEAVES

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Studies performed by our group have reported the significant anti-inflammatory and wound healing activities of the hexane fraction (HF) obtained from the crude extract of Pereskia aculeata Miller leaves. The major compounds identified in HF were sterols and triterpenes¹². Those results encouraged the evaluation of the in vivo topical toxicity of HF (Protocols COBEA nº013/2013, nº016/2013, and nº028/2014). An acute dermal irritation/corrosion test suggested by OECD¹ was performed using Wistar rats. The test group received topical application of HF 0.5 g, and the control group received only water. After 4 h, signs of edema and erythema were evaluated according to the Draize score system for 14 days. No topical toxicity was found. Also, the cutaneous atrophy was analysed, as it is a significant adverse reaction of the most effective topical anti-inflammatory drugs available. Swiss mice ears were topically treated with acetone 20 μL (vehicle), dexamethasone 0.1 mg/20μL or HF 1.0 mg/20μL for 7 days, twice a day. The ears thickness was measured using a digital caliper on day 1 and the end of the experiment. The topical use of dexamethasone significantly atrophied the mice ears, which was not observed for HF and vehicle. Although further studies are needed to evaluate the topical toxicity of HF better, those results suggested that its dermal application is safe. Previous studies had
reported that HF is as effective as dexamethasone\(^1\). However, the present work indicated that it did not cause cutaneous atrophy, which is a common adverse reaction of glucocorticoids, the primary drugs used for skin inflammation therapy.

**Financial support:** FAPEMIG, UFJF, CAPES, CNPq.

**References:**

**ANTIFUNGAL ACTIVITY AND PHYTOCHEMICAL CHARACTERIZATION OF BRAZILIAN SEMIARID PLANT SPECIES**

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Oral candidiasis is a fungal infection that affects the superficial epithelium of the oral mucosa, which is most often caused by the disordered growth of *Candida* spp. The most severe form of disseminated candidiasis may present 47% of mortality. Moreover, drugs used in antifungal therapy might present severe side effects. The use of plants for therapeutic purposes has been sought as an alternative to combat these disorders, presenting low cost and easy access. Nonetheless, this study aimed to evaluate the antifungal activity of medicinal plants' extracts from the Brazilian semiarid, as well as perform phytochemical characterization for the determination of total compound contents. Hydroalcoholic extracts of three species of medicinal plants, obtained by different methods (turbolysis, maceration and ultrasound) were analyzed. The following were evaluated: *Ximenia americana* L. (Olacaceae), *Schinopsis brasiliensis* Engler (Anacardiaceae), *Poincianella pyramidalis* (Tul.) L.P. Queiroz (Fabaceae). Minimum Inhibitory Concentration (MIC) was determined by broth microdilution technique against the *Candida albicans* (ATCC 18804). In the phytochemical characterization, colorimetric methods were used to detect and quantify total polyphenols, total flavonoids and condensed tannins. The tests showed antifungal activity against *C. albicans*. The lowest MIC obtained was 125 μg mL\(^{-1}\) relative to *X. americana* and *S. brasiliensis*. Quantitative phytochemical characterization revealed that the highest concentration of total polyphenols and condensed tannins found in *X. americana* extract. *S. brasiliensis* presented the highest concentration of total flavonoids. Therefore, we can conclude that the species tested have good antifungal activity and are promising to continue the development studies of new herbal medicines.
MODULATORY ACTIVITY OF ETHANOLIC AND FRACTIONATED EXTRACT OF Momordica charantia L AND BACTERIAL KINETICS AGAINST STRAINS OF Escherichia coli

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Scientific research has searched among plant species for specimens that may result in an innovative product to combat bacterial multiresistance. The population indicated *Momordica charantia* L. (Melão-de-São Caetano) for the treatment of several infectious diseases. This paper aims to evaluate the antimicrobial and modulatory activity of ethanolic extract and fractionated leaves of *M. charantia* against bacterial strains of *Escherichia coli* to determine the death curve of the strain under study in the presence and absence of the mentioned extract, and perform the phytochemical screening. The extracts were achieved by the cold maceration method. To obtain the fractions, the ethanolic extract was suspended in methyl alcohol and extracted exhaustively and successively using solvents of increasing polarities. Minimum Inhibitory Concentrations (MIC) were determined using the broth microdilution technique. In the phytochemical characterization, colorimetric methods were used to detect and quantify polyphenols and flavonoids. With the exception of the dichloromethane fraction, the others presented antimicrobial activity; the lowest MIC obtained was 0.0625 mg mL⁻¹. Regarding the modulating activity, the extracts acted synergistically to the antibiotic, reducing MIC of gentamicin. The ethanolic extract acted in the exponential phase reducing bacterial growth. The phytochemical characterization showed that all extracts have flavonoids and polyphenols, with emphasis on the concentration of 0.313 mg mL⁻¹ of flavonoids in the crude extract. The results achieved contribute to the enhancement of the information about the studied species and may be an option for the development of a phytotherapeutic with indication for infectious diseases.

IN VITRO EVALUATION OF A SEMISSOLID FORMULATION OF Schinopsis brasiliensis ENGLER WITH ANTIMICROBIAL ACTIVITY

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The treatment of skin burns is complex and requires special care in order to avoid mainly local and generalized infections. Plant species with antimicrobial activity may help in the microbiological treatment of these lesions. *Schinopsis brasiliensis* Engler is used in folk medicine as treatment for fungal and bacterial infections. In this context, the objective of this work was to evaluate the antimicrobial activity of *S. brasiliensis* extract and the efficacy of a semi-solid topical formulation produced from its dry extract. The extract was produced from a 70% (v/v) hydroalcoholic solution with the leaves of *S. brasiliensis*, and sprayed nebulized using colloidal silicon dioxide as a pharmacotechnic adjuvant. The extract was analyzed against ATCC strains of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Candida albicans* by broth microdilution technique to determine the Minimum Inhibitory Concentration (MIC). A compatibility study was carried out by different analytical techniques between the extract and excipients used in creams to obtain the formulation. Its effectiveness was tested by broth microdilution using the above-mentioned strains. The results showed that the extract was sensitive to all strains tested, being the most sensitive to *P. aeruginosa* with MIC of 0.031 mg mL⁻¹. To evaluate its efficacy, the cream was classified as active and moderately active against the analyzed species. Thus, it was possible to obtain a formulation from the dried extract of *S. brasiliensis* with proven antimicrobial activity in vitro.

Withdrawn by the author

Withdrawn by the author
ETHANOLIC EXTRACT FROM Commiphora leptophloeos (MART.) JB GILLETT LEAVES PRESENTS SPASMOLYTIC ACTIVITY ON WISTAR RATS

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Introduction: Commiphora leptophloeos is popularly known as “imburana” and used in the treatment of diseases such as bronchitis, colic and diarrhea. As the leaves ethanolic extract from Commiphora leptophloeos (CL-EtOHL) have already showed spasmolytic activity on rat ileum, we decided to investigate the spasmolytic effect in other smooth muscles (rat uterus, aorta and trachea). Methods: Wistar rats were used for experimental protocols. Isotonic and isometric contractions were recorded (n=3-5). All experiments were approved by the Ethics Committee on Animal Use of UFPB (Protocol 045/2016). Results and discussion: On rat uterus, CL-EtOHL (243-729 μg/mL) showed no significant inhibitory effect against phasic contractions induced by 10-5 M carbachol. Differently, when the contractions were induced by 10-2 IU/mL oxytocin the extract had a concentration-dependent inhibitory effect (IC50=246.1±59.8 μg/mL and Emax=84.9±6.1%), suggesting that CL-EtOHL may be acting at the level of oxytocin receptor. On rat aorta, CL-EtOHL (27-729 μg/mL) relaxed in the equipotent manner the pre-contracted organ with 3×10-7 M phenylephrine in the presence (EC50=219.4±28.5 μg/mL and Emax=79.6±8.4%) and absence (EC50=241.9±32.8 μg/mL and Emax=76.1±4.4%) of functional endothelium, discarding involvement of endothelium-derived relaxing factors in its vasorelaxant effect. Similarly, CL EtOHL (0.1-729 μg/mL) relaxed in the concentration-dependent and equipotent manner the trachea pre-contracted with carbachol in the (EC50=147.4±15.9 μg/mL and Emax=108.0±1.7%) of functional epithelium, also discarding the participation of epithelium-derive relaxing factors. Conclusions: CL EtOHL showed a non-selective spasmolytic activity on the organs tested, being more potent and effective in relaxing the rat aorta and trachea. Financial support: PIBIC/UFPB/CNPq.

EVALUATION OF THE ANTI-TRYPANOSOMA CRUZI ACTIVITY IN VITRO OF THE FLAVOLIGNAN SILIBININ

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Chagas’ disease (CD) is a neglected disease caused by the protozoan Trypanosoma cruzi. CD is originally endemic in Latin America and nowadays affects countries of several continents due to human migrations. Benznidazole (BZ), an imidazolyl compound, is the only drug available and used in Brazil to treat patients, it is a drug with limitations such as low efficacy at the chronic phase and several adverse reactions. Thus, the discovery of new drugs and therapies is needed. In this work, we evaluated the anti-T. cruzi activity of Silibinin (SLB), a natural flavanolignan derived from the milk thistle (Silybum marianum) plant, which has several medicinal uses reported, such as antioxidant, hepatoprotection, anti-cancer, anti-inflammatory, antiviral, anti-Leishmania protection, inhibition of cyp enzymes and P-gicoprotein activity, among others. Methods and Results: For trypanocidal evaluation, blood trypomastigotes forms of T. cruzi were treated with different concentrations (6.25, 12.5, 25, 50, 100 and 200 μg/mL) of SLB and, after 24 h the number of live parasites was counted in Neubauer’s chamber in parallel to Control, DMSO and BZ treated groups. For the cytotoxicity assay, VERO cells were seeded in 96-well plates and incubated with growing concentrations starting from smaller the effective one (100, 200, 400,800 μg/mL) of SLB. The toxic effect was assessed after 24 h by MTT. The results showed that SLB: i) was able to significantly reduce the number of free parasites in 54.22% and 69.88% at concentrations of 100 and 200 μg/mL, respectively; ii) showed IC50=250.76 μg/mL in VERO cells. It was demonstrated that its trypanocidal activity is similar to BZ at usual in vitro assay concentration (6μg/mL) and that SLB at concentration of 200μg/mL is significantly more active (18.07%) than BZ (which presents 51.81% of parasite reduction); iii) SLB was not toxic to the VERO cells at these concentrations with trypanocidal effect. Conclusion: Our data indicate that SLB presents trypanocidal activity and it opens new perspectives for CD treatment. Given the characteristics of SLB, further studies are being done associating BZ and SLB.
IN VITRO SCHISTOSOMICIDAL ACTIVITY OF THE EXTRACT OF Centaurea benedicta (Asteraceae)

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Introduction: Human schistosomiasis is an important neglected tropical disease and the most noteworthy parasitic disease after malaria which is responsible for more than 280,000 deaths annually. Treatment for this disease relies currently on a single drug, praziquantel (PZQ). However, concerns regarding PZQ resistance and insensitivity of juvenile schistosomes have increased the interest in resorting to medicinal plants as alternative drug therapies. Centaurea benedicta L. (Asteraceae) or popularly known as Blessed thistle, is an annual herb native to Mediterranean region and greatly distributed all over the Europe. In many countries this herb is well known as a traditional indigenous medicine such as tonic, antidepressant, anti-inflammatory, antibiotic and anti-Septic. The present study was designed to investigate the schistosomicidal activity of the extract of C. benedicta and its chemical composition by qualitative analysis. Methods: Fresh leaves of C. benedicta were extract with dichloromethane: ethanol (9:1) which produced 20g of extract. In vitro schistosomicidal assays were assessed against adult worms of Schistosoma mansoni in different concentrations 200 µg/mL, 100 µg/mL, 50 µg/mL and 25 µg/mL performed in 24, 48 and 72 hours. The extract analysis of C. benedicta was performed by UPLC-ESI-QTOF-MS. Results and discussion: All concentrations of the extract performed in different times of 24, 48 and 72 hours caused 100% mortality and significant reduction on motor activity of all adult worms of S. mansoni. Through UPLC-ESI-QTOF-MS five compounds were identified Cnicin, Oleanolic acid, Jacobisidin, Cirsimartin and Eupatorin. Conclusion: This study provides the first evidence for the schistosomicidal activity of the extract of C. benedicta. Opening a new source of potential compounds to be further studied as schistosomicidal agents.

Financial support and acknowledgement: The authors are grateful to FAPEMIG (PPM-00296-16) and CNPq for financial support, as well as to CAPES, PIBIC/CNPq/UFJF and CNPq for fellowships.

SPASMOLYTIC EFFECT OF THE CRUDE ETHANOL EXTRACT OF Sida rhombifolia L. (MALVACEAE)

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Introduction: Sida rhombifolia L., popularly known as “mata-pasto” and “relógio”, presents wide ethnomedicinal use in the treatment of several diseases, such as diarrhea, asthma and hypertension. As the crude ethanolic extract obtained from Sida rhombifolia L. aerial parts (SR-EtOHₐ) has already demonstrated anti-diarrheal activity in mice and spasmolytic activity in the rat ileum, we decided to investigate the spasmodic effect in other smooth muscles (rat uterus, aorta and trachea). Methods: Wistar rats (Rattus norvegicus) were used. Isotonic and isometric contractions were measured. All experiments were approved by the Committee Ethics on Animal Use of UFPB (Protocolo 045/2016). Results and discussion: On rat uterus, SR-EtOHₜₐ (243 µg/mL, n=3) presented a low inhibitory effect only on carbachol 10⁻⁵ M (Eₘₐₓ=23.5±4.3%). On rat aorta, SR-EtOHₜₐ (1-729 µg/mL, n=5) inhibited in a concentration-dependent manner the tonic contractions induced by 3x10⁻⁴ M phenylephrine, being more potent in the presence (Eₘₐₓ=37.3±5.9 µg/mL and Eₘₐₓ=87.5±5.2%) that absence (Eₘₐₓ=78.4±2.9% and EC₅₀=67.7±11.9 µg/mL) of functional endothelium, suggesting the participation of endothelium-derived relaxing factors in its vasorelaxant effect. Similarly, SR-EtOHₜₐ (0.03-243 µg/mL, n=5) relaxed the trachea pre-contracted with 10⁻⁶ M carbachol more potently in the presence (Eₘₐₓ=26.1±3.9 µg/mL and Eₘₐₓ=113.0±4.0%) than absence (EC₅₀=243.3±39.6 µg/mL and Eₘₐₓ=102.9±2.9%) of functional epithelium, also suggesting the participation of epithelium-derived relaxing factors in its relaxant effect. Conclusions: SR-EtOHₜₐ showed a non-selective spasmodic activity on the organs tested, being more potent and effective in relaxing the rat aorta and trachea, through endothelium- and epithelium-derived relaxing factors, respectively.

Financial support: PIBIC/UFPB/CNPq.
Introduction: Phytotherapy is based on the use of plants as medicines. It uses parts of plants such as leaves, stems, roots, flowers and seeds with known pharmacological effect. Banana, (Musa spp., Family Musaceae), has great nutraceutical value and high levels of antioxidants. Therefore, the objective of this work was to evaluate the stability of a mother-tincture produced with the banana inflorescence, through its antioxidant activity. Methods: Following the protocol of the National Agency of Sanitary Surveillance (Anvisa), a mother-tincture was prepared with 100g of inflorescence and 120ml of cereal alcohol, being infused for 14 days. The sample was then filtered and stored in amber glass. Using the method that evaluates the antioxidant capacity through the sequestering activity of 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical. The reaction was performed by spectrophotometry at 515 nm and monitored at 0, 15, 30, 45 and 60 minutes, right after filtration, at 30 days and at 12 months. Results and discussion: The average antioxidant activity of mother tincture was 59%. At 30 days of 34% and in 12 months it was 31%. When presenting polyphenols and some reducing agents like thiols, bananas are rich in antioxidants, whose function is to inhibit the oxidation of other molecules, reducing free radicals and cellular oxidative damage. Moreover, in its composition we find a sufficient amount of other biologically active substances that are documented in traditional and scientific literature making it a medicinal plant, with many pharmacological properties like antifungals, antioxidants, antiallergics, anti-inflammatory, regulator of the intestine, anticarcenogenic and hepatoprotectors. Conclusion: The mother-tincture with the inflorescence of the banana revealed a high antioxidant content and its stability suffered little loss during the analyzed period, in this way, the natural antioxidant property of this flower can be a good substitute for the synthetic, beyond contributing to the prevention of other diseases.

COPAIBA OIL SUPPRESSES INFLAMMATORY PROCESS IN ALLERGIC ASTHMA ANIMAL MODEL

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Introduction: Asthma is a common disease of the airways, considered a public health problem, capable of causing expensive costs for health systems. Problems related to the difficulty of access to treatment besides low adherence and risk of low responsiveness justify the research of new compounds. Copaiba oil is an alternative already widely used in folk medicine, but not yet scientifically studied for the treatment of the disease. We investigated immunomodulatory effects of CO on BALB/c mice induced with allergic asthma model with Ovalbumin (OVA). Methods: The investigatet oil had its composition verified by CG-FID and CG-MS. Mice were treated at the dosages 50 mg/kg and 100 mg/kg/day. After the induction of allergic asthma, the anti-inflammatory potential of CO was evaluated by counting and differentiating the inflammatory cells in the BAL, free radical (NO) analysis and cytokine of CO treatment significantly ameliorated 1 2 1 responses, mainly IL-4, IL-17 and TNF-α. In the treated animals there was also a reduction of the inflammatory infiltrate in the lung tissue, with a decrease in the density of the alveolar parenchyma. Conclusions: These results support the use of CO as a promising compound for the study of new therapies for the treatment of asthma. However, new studies need to be done to support this idea.

Acknowledgements: This study was supported by Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG Grant n° CDS - APQ-02753-16)
TREATMENT EVALUATION OF A LACTONE SESQUITERPENE AGAINST *Trypanosoma Cruzi*: IN VITRO AND IN VIVO STUDY IN EXPERIMENTAL CHAGAS’ DISEASE

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Chagas disease (CD), originally present in Latin America, remains neglected and nowadays autochthon in other Continents. The only drug available to treat CD in Brazil is benznidazole (BZ), which presents several limitations. This project aims the use of conventional formulations of lactones sesquiterpenes (LS), previously active against *Trypanosoma cruzi* in vitro, with the following objectives: to develop new formulations of LS for oral administration, evaluate its toxicity and effectiveness against *T. cruzi* infection in vitro and in vivo. For evaluation of cytotoxicity in H9c2 cardimyoocytes cells, MTT and Neutral Red (NR) assays were performed and, for in vivo, biochemical and hematological parameters were evaluated. To check the activity of the LS against the *T. cruzi*, H9c2 were infected with strain of *T. cruzi* and were treated for 24 and 48 hours to efficacy evaluation. To evaluate the in vivo assay, mice were infected with *T. cruzi* Y strain and treated with intravenous (IV) and oral route for 20 consecutive days with the doses of LS 1.0; 5.0 and 25.0 mg/kg/day and control groups (BZ and infected not treated animals). Parasitemia levels were evaluated for 45 consecutive days. The treatment efficacy was evaluated by parasitological (hemoculture and PCR) and serological (ELISA) assays. The results obtained so far revealed citotoxicity above 250ng/mL in H9c2 cells treated for 24 and 48h in both MTT and NR tests. For in vivo assays, there were no signs of nephrotoxic and hepatotoxic activity in the assayed doses of 50 and 100mg/kg of LS. A low toxicity was revealed in vivo by the low levels of analyzed parameters in this doses. The parasitemia analyzes showed significant decrease starting at the 5th day of treatment with LS at 1mg/kg/day IV and oral route; 5mg/kg/day oral route and BZ compared to control group INT. The survival rates of mice with LS were 100% with the dose 5 mg/kg/day, followed by 1.0 mg/kg/day IV and BZ, which were 87%. The control group INT showed only 25% of survival until the end of the evaluation. None of the mice were cured when analyzed the serological testes because of the difficulty of getting the decrease levels of antibodies titles in this model, but all mice treated with the 5mg/kg/day dose had negative parasitological assays with 100% of survival. These findings represent a great perspective for treatment of CD and further new formulations involving nanocarriers will be explored in order to achieve a better treatment efficacy.

PROTECTIVE EFFECT OF CINNAMALDEHYDE ON GASTRIC INJURIES INDUCED IN MICE

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**Introduction:** *Cinnamomum cassia* is widely used in Chinese medicine and is indicated for diseases digestive systems. The aim study is evaluated the gastroprotective effect of Cinnamaldehyde against ethanol-induced gastric in Swiss mice and verified its antioxidant mechanisms. **Methods:** Animals were separated into Five groups: Control (C); ulcerated (U); Lanzoprazol treated (L; 3mg/kg) and Cinnamaldehyde at 20 (CN20) and 50 mg/kg (CN50), all treatments were keep for 14 days. At 14th day, the ulcer were induced and the animals were euthanized and organs were removed. Stomach was used for macroscopical evaluation of lesion and a homogenate was performed to determine antioxidant (SOD and Catalase) and protein and lipid oxidation (CEUA:434-2017). **Results and discussion:** Treatment with CN promotes macroscopical gastroprotection into a similar to lanzoprazole (p>0.05). Additionally, CN treatment decrease protein oxidation (C:44.11±9.04; U:82.62±6.00; L:55.95±2.12; CN20:52.89±2.42; CN50:52.75±3.74 chloramineT/mg protein), lipid peroxidation (C:0.0017±0.0002; U:0.0022±0.0005; L:0.0018±0.0005; CN20:0.0016±0.0001; CN50:0.0017±0.0002 mmolMDA/mgprotein) and improve antioxidant enzymes activity SOD (C:107.4±12.7; U:38.9±8.9; L:83.1±9.2; CN20:93.9±5.9; CN50:107.1±13.9) and CAT (C:6.12±1.22; U:0.96±0.21; L:4.56±1.77; CN20:3.86±0.95, CN50:2.77±1.15). **Conclusions:** Treatment with cinnamaldehyde was able to protect the development of gastric lesions and promote decrease on oxidative stress.
RENEALMIA PETASITES

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Introduction: The Brazilian traditional medicine uses plant species for the treatment of various diseases, and many of them have little or no scientific study. In this situation is the Renealmia petasites. This species, present in the Atlantic Forest belongs to the Zingiberaceae family. The species, known as “pacová”, is of pharmaceutical, ethnobotanical and economic importance in some regions of Brazil. In the literature, there are reports of the association between its traditional use and its mineral composition, as well as reports on the use of the species as anthelmintic, antirheumatic and for stomach and intestinal diseases. Methods: It was performed the maceration from 2 kg of the fresh rhizome of R. petasites using about 4 L of ethanol P.A as the solvent. After 72 hours of extraction, the ethanolic extract was filtered and freeze-dried. Then a 1: 1 methanol-water suspension was prepared and extractions with hexane, dichloromethane and ethyl acetate were performed. Antioxidant activity tests with the crude extract and its fractions using the method of free radical sequestration 2,2-diphenyl-1-picrylhydrazyl (DPPH method), phosphomolybdenum complex and β-Carotene / linoleic acid systems were performed. The determination of total phenolics was performed using the Folin Denis method. Results and discussion: The antioxidant activity was found in the fractions in dichloromethane and ethyl acetate. In DPPH method, this fractions demonstrated in the concentration of 62, 5 μg/ml an inhibition of 95% when compared to the quercetin standard in the same concentration. Besides that, at phosphomolybdin complex the antioxidant capacity the dichloromethane fraction was about 60% when compared to ascorbic acid standard and 80% to quercetin standard, in addition, the ethyl acetate fraction showed 40% the antioxidant capacity compared ascobic acid standard and about 65 % as to quercetin standard. However, the results have shown that less than 3% of phenolic substances were found in these fractions, suggesting that non-phenolic substances may be responsible for the antioxidant activity observed. Conclusions: In conclusion, from this results, it was observed the great antioxidant potential of the R. petasites and in the future its possible use in several inflammatory diseases.

CHROMATOGRAPHIC PROFILE AND IN VITRO EVALUATION OF ANTIOXIDANT POTENTIAL OF Siparuna guianensis Aublet

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Introduction: The species Siparuna guianensis Aublet (Siparunaceae), popularly known as “negramina”, “capitú”, “hoja-santa” and “lemon-bravo” are distributed throughout the Brazilian territory and have been used in folk medicine to combat fever, inflammation, body aches and other disorders. Many diseases can lead to the formation of free radicals and oxidative stress that are associated with inflammatory processes. Thus, the objective of this work was to evaluate the antioxidant activity of the dichloromethane partition (DCMP) obtained from S. guianensis leaves and to elucidate the presence of phenolic compounds that may have antioxidant activity. Methods: Free radical 2,2-difenil-1-picrilhidrazil (DPPH) reduction and inhibition of the lipid peroxidation process (β-carotene /linoleic acid method) were tested to investigate the antioxidant activity of DCMP. The chromatographic profile of DCMP was obtained by UV-HPLC. Results and discussion: DCMP and the reference compounds, quercetin, and ascorbic acid, were able to reduce 50% of DPPH radical at concentrations of 25.1 ± 2.19; 1.31 ± 0.14 and 0.23 ± 0.02 μg/mL, respectively. Regarding the linoleic acid peroxidation method, DCMP presented a dose-dependent inhibition. as in the highest concentration (222 μg/mL) it presented the highest inhibition percentage (63.54%). In contrast, at the lowest concentration (9.50 μg/mL), a reduction of inhibition (16.44%) was observed. The reference compound quercetin was able to inhibit 83.63% and 71.21% of peroxidation peroxidation at the highest and lowest concentration, respectively. The antioxidant activity observed for DCMP can be attributed to the flavonols found in the chromatogram, identified by their characteristic UV spectra. Conclusion: Considering the results obtained in both antioxidant methods, it can be inferred that DCMP has promising antioxidant potential. Financial support: FAPEMIG, UFJF, CAPES, CNPq.
ANTIBACTERIAL AND ANTIBIOFILM ACTIVITY IN Trichoderma AND Aspergillus STRAINS ASSOCIATED TO MARINE SPONGES FROM NORTHEAST BRAZIL

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Introduction: Natural products structures continue to play a highly significant role in drug discovery and development process, and approximately 60% of the drugs on the market are derivatives based on or made directly from natural products. With increased pressure on existing antibiotics and the subsequent emergence of multidrug-resistant strains, the ability to develop novel effective antibacterial agents is proving challenging. Bacteria that attach to surfaces aggregate in a hydrated polymeric matrix to form biofilms, and the formation of these sessile communities and their inherent resistance to antimicrobial agents are at the root of many persistent bacterial infections. Marine organisms live in a very exigent, competitive and aggressive surrounding, which demands the production of specific and potent molecules that can be potentially active against persistent bacterial infections.

Objective: This study aimed to access and evaluate antibacterial and antibiofilm activity in extracts obtained from Trichoderma and Aspergillus strains associated to marine organisms.

Materials and methods: Marine sponges and zoanthids were collected in Ponta Verde, Maceió, and microorganisms associated were isolated and identified. Four Aspergillus spp. and four Trichoderma spp. strains were selected and grown for 14 days. Mycelium was extracted with methanol, and metabolic products were fractionated with ethyl acetate to obtain another two fractions (aqueous and organic). Each of the three fractions obtained from each of the eight fungi species were tested against Pseudomonas aeruginosa ATCC 27853 and Staphylococcus aureus ATCC 25904, and antibacterial and antibiofilm activity were accessed by OD600 and crystal violet assay, respectively.

Results and discussion: The in vitro screening has shown that the strains evaluated presented antibacterial and/or antibiofilm activity against Pseudomonas aeruginosa ATCC 27853 and/or Staphylococcus aureus ATCC 25904 in one or more of the extracts obtained. Planktonic bacterial growth was significantly inhibited by five fractions tested, when compared to untreated control (p>0,05). And four fractions were able to inhibit in at least 50 % biofilm formation.

Conclusions: The results obtained in this screening show the potential of marine microorganisms as a source of antibacterial and antibiofilm compounds.

THE TOXICOLOGICAL EFFECTS LUFFA OPERCULATA: A REVIEW

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The Luffa operculata (L.) Cogn. is widely used in folk medicine for the treatment of sinusitis. When used excessively, may expose an individual to serious health risks, and their inappropriate use can be potentially toxic. The objective of this study was to verify the characteristic adverse effects of the plant. The systematics used was a bibliographical research. Indexed works were evaluated in the databases SciELO, CAPES, Lilacs, Science Direct and PubMed, from 2010 to 2018. As result was observed that Luffa operculata (L.) appears between plants with the highest number of citations related to adverse reactions and/or poisoning. The main adverse reactions cited in the works studied were related to your abortive effect, raised by the curcubitacinas, responsible for the embryotoxic actions and abortion. Besides that, has been found cytotoxic effects of the vegetable at concentrations greater than 500 ug/mL, or approximately 1g of vegetable extract can be lethal for a 70 kg adult. Nosebleeds can also happen, they are a result of nasal aspirations or topical application of “concentrates” of cooking, and can cause intense inflammatory reaction and mucosal injury, worsening respiratory symptoms nasosinusais. Other adverse reactions include nausea, vomiting, abdominal pain, headaches, bleeding, coma and death. Therefore, it is necessary to larger studies regarding the purpose and forms of use in which the L. operculata can be employed being effective, as well as the study of non-toxic dose to the body, so that it can propagate this knowledge to prevent future adverse reactions.
EVALUATION OF ANTIOXIDANT ACTIVITY FROM SERICINA

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Introduction: Several works developed in animal models in the last decades have demonstrated the high antioxidant potential of sericin, natural polymer obtained from silkworm, discarded as industrial waste in the production of silk. The objective of this study was to evaluate the antioxidant activity of sericin for use in nutritional formulations. Material and methods: The antioxidant activity was performed by the capture of the radical 2,2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS •+) with different volumes (30, 60, 90 µL) of sericin at 0.5%. The results were compared with the positive butylhydroxytoluene (BHT) standard at the same concentration (0.5%) and volume of the triplicate sample. Results and discussion: During the (ABTS-•+) assay, the antioxidant activity increased proportionally from 30, 60, 90µL (13.49; 22.73; 37.67% respectively). At 90µL it was observed a relatively high activity when considering the concentration of the sample and the small volume used. However, it was lower than the positive BHT standard at 90µL (87.71%). Conclusion: The large amount of terminal hydroxyls present in the amino acids constituting sericin allows the interaction with free radicals and cationic ions by complexation mechanisms, which explains the antioxidant activity of this compound. In this way, the protein is indicated as a molecule of choice in the prevention of oxidative stress, and can be used in combination therapy with other non-enzymatic antioxidants in nutritional formulations. Acknowledgments: To CAPES, FUNDAÇÃO ARAUCÁRIA and UNIOESTE.

PRELIMINARY STUDY OF NOVEL ANTI-TUMORAL TRITERPENES EXTRACTED FROM CHILEAN NATIVE PLANTS

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Introduction: Therapeutic agents derived from plant triterpenes have become an important group of phytochemicals for the pharmaceutical industry, due to their biological properties (anti-inflammatory, anti-bacterial, anti-tumor and adjuvant). Their structural diversity could suggest a relationship between triterpene structure and the diverse biological activities of this class of molecules. Several studies have revealed that triterpenes have a great potential as anti-tumor therapies, because they alter biological membranes, specifically cholesterol, and could affect diverse cellular activities including regulation of the cell cycle, proliferation and apoptosis. Methods: In the current work, three triterpenic molecules were evaluated, QA, QS21 and QSQ, purified from plant extracts by chromatographic methods. Cytotoxicity and anti-tumor potential of molecules were determined by MTS assay. The property to induce apoptosis of these molecules was evaluated by TUNEL, Annexin V and caspase activity were measured by flow cytometry on an in vitro model of human gastric cancer, using SNU1, AGS and KATOIII cell lines. Results: The three molecules evaluated showed an IC50 less than 50 µM for treatments of 24h and 48h. Normal epithelial gastric cells, GES1, showed lower inhibition of cell proliferation as compared to the cancer cell lines. All molecules showed the ability to induce apoptosis on cancer cells as determined by flow cytometry. Discussion and conclusions: Further studies are required to evaluate the mechanism of apoptosis of these triterpenes on gastric cancer cells. These preliminary results are exciting because they suggest a novel treatment for gastric cancer, using natural compounds extracted from a native species of Chile.
HOST-GUEST INTERACTION OF THYMOL WITH β-AND HYDROXYPROPYL-β-CYCLODEXTRIN: PREPARATION AND PHYSICOCHEMICAL CHARACTERIZATION

LANA NAIADHY SILVA SANTOS, YASMIM MARIA BARBOSA GOMES DE CARVALHO, CAIO ALCÂNTARA CAMPOS, ANA CLARA RAMOS, BRUNO SANTOS LIMA, LUCINDO JOSÉ QUINTANS JÚNIOR, PAULA DE CÁSSIA ANDRADE DE SANTANA, ELIANA MIDORI SUSSUCHI, LUÍZA ABRAHÃO FRANK, SILVIA STANISCIUASKI GUTERRES, LUCIANA SCOTTI, PAULO CESAR DANTAS DA SILVA, JOSÉ ROLIM NETO, ADRIANO ANTUNES DE SOUZA ARAÚJO, MAIRIM SERAFIINI RUSSO

Introduction: Thymol (TM) is a phenolic compound with various pharmacological activities elucidated in the literature. With the strategy of improving their physicochemical properties and preserve the therapeutic potential, this study aimed to prepare and characterize complexes inclusion of TM/β-CD and TM/HPβ-CD. Methods: The samples were prepared with βCD and HPβ-CD by freeze-drying (FD) method in molar ratios of 1:1. Molecular docking, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), Karl Fischer titration (KFT), thermogravimetric analysis (TG/DTG), Fourier-transform infrared spectroscopy (FTIR) and entrapment efficiency (EE%) by high performance liquid chromatography (HPLC) were used for the characterization of the complexes. Results and discussion: The docking showed possible formation of inclusion complexes with favorable energy (-3.45 kcal.mol⁻¹) for both CDs. The SEM images showed that reduction in the crystal structure of TM exhibited smaller crystals with different morphology for TM/βCD and TM/HPβ-CD. Corresponding DSC curves TM/β-CD and TM/HPβ-CD did not show any endothermic peak in the temperature range of TM volatilization, indicating the inclusion of TM inside cavity complexes and TG/DTG curves showed mass loss both for TM/β-CD as for TM/HPβ-CD with 8.89% and 5.61%, respectively (115-325°C). FTIR analysis evidences a strength interaction among thymol and each of the CDs (β-CD and HPβ-CD), the spectrum showed variations in intensity and bands between 944 cm⁻¹ and 807 cm⁻¹. The EE% obtained was 65% for β-CD and 60% for HPβ-CD. Conclusions: The results showed that TM formed inclusion complexes with both CDs, mainly with TM/β-CD. This study can contribute to other studies involving this type of system.

OPHTALMIC APPLICATION AND EVALUATION OF COROSOLIC ACID TOXICITY

CIBELE TOLEDO, VINÍCIUS PEREIRA, LAYS DOURADO, MAYARA PAIVA, ARMANDO SILVA-CUNHA

Introduction: Corosolic acid (CA) is a natural pentacyclic triterpene occurring in a variety of medicinal plants and exhibits numerous biological properties, such as: antiangiogenic, antiadipetic, antioxidative, antiinflammatory and antiproliferative activities. This study aimed to investigate the ophthalmalic application of CA, evaluating the citotoxicity and the safety of intravitreal administration of CA using in vitro and in vivo models. Methods: Cytotoxicity effect of CA was evaluated in ARPE-19 cells by sulforhodamine B colorimetric method. An amount of 0.01 mL of CA formulations at 5, 10 and 25 μM was injected in the right eyes of Wistar rats and the contralateral eyes received the vehicle to verify the safety of ophthalmic use. Full-field electroretinography (ERG) was applied to evaluate the retinal activity and, therefore, the safety of intravitreal injection of CA. ERG recordings were performed before, 7 and 15 days after the intravitreal injection. Animals were sacrificed on the 15th day and the histological analysis of retina was carried out under light microscopy. Results: CA did not present cytotoxicity for ARPE-19 cells at concentrations below 35.5 μM after 48 hours of treatment. ERG recordings and histological evaluation did not show any signs of retinal toxicity. Conclusions: CA revealed safety for potential ophthalmic use and may be an useful alternative in the therapy of ocular diseases. Ethical Approval: All experiments were carried out in accordance with the statement of Association for Research in Vision and Ophthalmology (ARVO) for the Use of Animals in Ophthalmic and Vision Research and were approved by the Ethics Committee on Experimental Animals of UFMG (Protocol nº 227/2017). Acknowledgments: CAPES, CNPq, FAPEMIG.
EVALUATION OF THE ANTIBIOTIC ACTIVITY OF KAVA-KAVA DRIED EXTRACTS

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Introduction: Reports about the antibiotic activity of aqueous and hydroalcoholic kava-kava dried extracts from leaves and rhizome, respectively, can be found in literature. However they do not refer to the currently commercial available rhizome extract (ethanolic). For that, we aimed to evaluate the antibiotic activity of ethanolic extracts of the kava-kava rhizome obtained from different compounding pharmacies in Minas Gerais. Methods: For this study were tested eight species of bacteria and fungi each. Seven extracts were evaluated and the microorganism’s susceptibility to them was determined by the minimum inhibitory concentration (MIC) using the methodologies: M7-A9 (bacteria), M27-A3 (yeasts), M38-A2 (filamentous fungi) and modified M38-A2 (dermatophyte fungi), from the Clinical and Laboratory Standards Institute. The extracts and the D,L-kawain standard were first solubilized in dimethylsulfoxide, followed by successive dilutions in the microorganism respective culture media. Results and discussion: The extract samples and the standard evaluated do not possess antibacterial activities against the bacteria analyzed. For the majority of the evaluated fungi there was no growth inhibition, with the exception of Cryptococcus spp., whose MIC values varied according to the species, lineages and extract samples (samples 3, 4, 6, 8 and 12). The kava-kava extract sample number 4 presented the lowest MIC values in the study. Since it was not observed growth inhibition for any of the tested microorganisms by the D,L-kawain standard, there is an indication that the inhibition generated by the extracts was not caused by this biomaker but by another substance present in the extracts. Conclusion: The evaluated extracts do not possess antibacterial activity against the tested bacteria in this study. Regarding the antifungal activity, the growth inhibition of Cryptococcus spp. was verified in the presence of five kava-kava extract samples, demonstrating its variability. The MIC values obtained against Cryptococcus were still considered to be high, rendering continuity of tests unnecessary. Financial support and acknowledgements: CAPES, FAPEMIG, Farmacopeia Brasileira and ANVISA.

INTESTINAL PERMEABILITY OF COPALIC AND KAURENOIC ACIDS USING CACO-2 CELLS

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Introduction: The use of copaiba oleoresin in folk medicine is due to its anti-inflammatory and antiseptic activities being used in the treatment of bronchitis, syphilis, skin diseases and ulcers. The pharmacokinetic properties of copalic acid (CA) and kaurenoic acid (KA), the two major diterpenes of oleoresin, have not been described. This study aimed to evaluate the permeability of CA and KA using the in vitro Caco-2 cells model which a predictive test for oral drug absorption. Methods: Resazurin assay was carried out to evaluate the cell viability of the evaluated compounds. Caco-2- cell monolayers were cultivated for 21 days in Transwell® plates for in vitro permeability assays. The integrity of the monolayers was examined by measuring the transepithelial electrical resistance (TEER). CA and KA were determined by a validated method using high performance liquid chromatography with mass spectrometry detection (LC-MS). Apparent permeability values (Papp) were determined from the amount permeated through the Caco-2 cells membranes at the apical-basolateral direction. Results and discussion: Only cell monolayers with a TEER above 200 Ω × cm² were used for the transport assays. Cells were considered viable when incubated at the concentrations used in the permeability test (3.9 mM) for 24h. CA and KA exhibited moderate permeability with Papp values of 4.67 × 10⁻⁶ cm/s and 4.66 × 10⁻⁶ cm/s. Conclusions: CA and KA presented moderate intestinal permeability. The Papp values show that both diterpenes present great potential as new drug candidates for oral administration. Acknowledgements: CAPES, FAPESP (14/50265-3).
GELATIN MEMBRANES WITH USNIC ACID FOR TOPICAL TREATMENTS FOR CUTANEOUS LEISHMANIASIS

MARIA JOSIEL MELO DE JESUS, LUCIANA GARCEZ BARRETTO TEIXEIRA, BRUNO DOS SANTOS LIMA, TIAGO DA SILVA NUNES, DIEGO MOURA TANAJURA, ADRIANO ANTUNES DE SOUZA ARAÚJO

Introduction: The therapeutic options limited to the treatment of Leishmaniasis increase the researches by the development of a new alternative. Therefore, our research group is expanding the current knowledge on the leishmanicidal activity of usnic acid and we have the objective to evaluate the therapeutic potential of gelatin membrane containing usnic acid (UA) as a topical treatment of cutaneous leishmaniasis. Methods: To obtain the membrane, UA was incorporated in liposomes, which was placed into gelatin solution and kept under magnetic stirring for 24 hours. Parasitic viability was determined from L. braziliensis (V.) axenic promastigotes, which was exposed to membranes containing UA. In vitro cytotoxicity study was carried out with healthy human macrophages (L929) strains (approval protocol: 92197218.8.0000.5546). The membranes were co-incubated for 24 and 48 hours at 37 °C, 5% CO2 and the total number of viable cells was estimated. The treatment of the infected human macrophages by L. braziliensis (V.) with membranes containing UA was evaluated from the number of infected cells and intracellular amastigotes. All membranes added to the test cultures contained different concentrations of UA (0.4, 0.8 and 2.0 μg/ml) and the control cultures were incubated with membranes without AU. Results and discussion: It was possible to observe the leishmanicidal activity of the test membrane with the significant reduction of infected cells and the healthy cells exposed to the membrane no showed reduction in cellular viability. Conclusions: The results demonstrated the promising use of gelatin membranes containing UA as a new formulation for the topical treatment of cutaneous leishmaniasis.

ACHYROBICHALCONE AND 3-O-METHYLQUERCETIN ISOLATED FROM Achyrocline satureioides PROMOTE APOPTOSIS IN MDA-MB-231 HUMAN BREAST CANCER

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Introduction: Achyrocline satureioides inflorescences contain main three flavonoid-aglycones, known as quercetin (QCT), luteolin (LUT), and 3-O-methylquercetin (3O MQ)1,2,3, besides a bichalcone named achyrobichalcone (ACB)4. ACB has a unique chemical structure that has not been described in other plants4. Thus, the aim of this study is to obtain ACB and 3O MQ from A. satureioides using high performance counter current chromatography (HPCCC) and, using the human breast cancer cell line MDA-MB-231, analyze a possible mechanism by which these compounds could interfere with cell cycle control and induce cell death. Methods: ACB and 3O MQ isolation was performed in two HPCCC steps. Additionally, the effects of compounds on cell viability in breast cancer cells lines (MDA-MB-231) and breast normal cell line (MCF-12A) were evaluated. A possible mechanism by which ACB and 3O MQ could interfere with cell cycle control and induce cell death were analyzed. Results and discussion: ACB and 3O MQ presented purity of 98.4 and 97.1% (w/w), respectively. The results show that inhibited ACB and 3O MQ cell proliferation and viability in MDA-MB-231 cell line, apoptosis was induced in a concentration manner. Cytotoxic effects of ACB presents selectivity index greater than 2. 3O MQ also had cytotoxic effect, however with a lower selectivity index. ACB and 3O MQ induced caspase-3, -7 and -9 activation in MDA-MB-231 cell. Conclusions: The results suggest that apoptosis in MDA-MB-231 cell was induced through a caspase-dependent intrinsic pathway. Being more selective than 3O MQ, ACB could be a potent candidate as novel anticancer agents acting on human breast.

Financial support: Brazilian Government research agencies: CNPq, CAPES e FAPERGS.

References:
ISOLATION AND IDENTIFICATION OF A HALOGENATED SESQUITERPENE FROM THE RED ALGA LAURENcia Catarinensis

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Introduction: Marine-derived natural products present an interesting structural diversity and great therapeutic potential. Red algae belonging to the Laurencia complex are capable of producing an enormous diversity of secondary metabolites, including terpenes from various classes, and acetylgenes. A large number of studies have shown that these metabolites exhibit promising biological activities. The first investigation of the species Laurencia catarinensis from the coast of Santa Catarina was performed with a sample from Arvoredo Island, leading to the isolation of caespitol, a cytotoxic halogenated sesquiterpene and related metabolites. In later study, with sample collected from Xavier Island, seven chamigrane-type halogenated sesquiterpenes and two acetylgenes were isolated; some were new reports to the species. The interesting potential on chemical diversity presented by L. catarinensis motivated to continue the chemical investigation of the species from the Brazilian coast.

Methods: A new sample of the algae, collected from Xavier Island, was soaked in dichloromethane/methanol 2:1. The extract was fractionated by successive chromatographic separations. Fractions and the isolated compound were monitored by thin layer chromatography and analyzed by spectroscopic methods.

Results: As a result, we report the isolation of the sesquiterpene 2,10-dibromo-3-chloro-7-chamigrene, unprecedented for the species. This compound has been reported for other Laurencia species and has demonstrated biological activity against Mycobacterium tuberculosis and toxicity in Artemia salina bioassay.

Conclusion: The discovery reassures the capacity of L. catarinensis in diversifying the production of secondary metabolites, which might present interesting biological potential.

Acknowledgements: We would like to thank CAPES, CNPq and PPGFAR/UFSC for financial support.

FATTY ACID PROFILE, PHYSICOCHEMICAL AND THERMAL CHARACTERIZATION OF THE COLD-PRESSED Campomanesia adamantium Cambess. SEED OIL

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Introduction: The Campomanesia (Myrtacea) found in Cerrado biome in Mato Grosso do Sul State, Brazil, is a human potential food in natura, homemade liqueurs, juices and sweets. The seeds are the wasted resources not used for human food. The aim of this study was to determine the profile of C. adamantium seed fatty acids (FAs), phytochemical characterization and thermal analysis.

Methods: Gas chromatography, thermogravimetric analysis and differential scanning calorimetry were used to determine the profile of FAs, evaluate the quality decomposition under heating time and temperature, and crystallization and melting of oil, respectively. To evaluate the oil quality, phytochemical analyses were performed by iodine, acid, saponification, peroxide, refractive, density, lipid, DPPH, nutritional quality indices and characterization by UV-Vis. Results and discussion: The FAs (24) were identified, palmitic acid with (32.92%), followed by oleic (23.92%), linoleic (3.35%), palmitoleic (2.72%) and stearic (1.79%) acids. In addition, long-chain fatty acids (LCFAs) with (66.24%), followed by short-chains (SCFAs) (32.03%) and medium-chains (MCFAs) (0.43%) fatty acids. LCFAs are anti-inflammatory, antibacterial, act on cardiovascular disease (CVD), coronary heart disease (CHD); SCFAs benefit intestinal health, stimulating blood flow, electrolyte uptake, furnace colonocytes energy, present anti-inflammatory, anti-carcinogenic, immune regulation to metabolism in tissue/organ; MCFAs are associated with dental caries, CHD, CVD risk and decrease high-density low-cholesterol, reduce lipase activity in the intestine. The results of the evaluated indices and thermal analysis range as in the several worldwide edible oils. Conclusion: We concluded that C. adamantium seed oil is a potential candidate resource for food products and soap making.
PHYTOCHEMICAL DETERMINATION AND EVALUATION OF PHOTOPROTECTIVE POTENTIAL FROM EXTRACT OF Bauhinia sp.

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Introduction: The development of products that use natural composts with antioxidant activity has been the focus of many researches. Thus, the phenolic compounds and flavonoids present in the Bauhinia extract might be an important source for the reduction of the oxidative stress caused by exposure to sunlight. The aim of this work was to evaluate quantitatively the phenolic compounds present in the extract of the pericarp of Bauhinia sp. and verify the photoprotective potential in the UVB region.

Methods: Five dermocosmetic bases usually used for sunscreens were prepared and compared with commercially available sunscreens. Spreadability and pH determinations were employed to select the dermocosmetic basis (DB) used to add UV filters in order to obtain SPF 15. The photoprotective activity was measured through spectrophotometric assays according to the adapted Mansur method using 5.0 % (w/w) of hydroethanolic extract from the pericarp of the plant. Results and discussion: The pericarp extract yielded obtained by maceration at a concentration of 0.02% to phenols, tannins and flavonoids was 161 µg/g, 112 µg/g and 253 µg/g, respectively. It was noted that the pH of DB changed after adding the extract (6.14 to 5.55). The spectrophotometric reading of the dermocosmetic basis associated with UV filters and the Bauhinia sp extract for the SPF was 19.94 ± 0.05. Conclusions: The extract can be positively used in photoprotective preparations as adjuvants, associated with synthetic filters. Its filtering ability in isolation is significant, and may come to collaborate with future sunscreen formulations.

Financial support: UFSJ.

IMMUNOMODULATORY ACTIVITY OF Musa x paradisiaca EXTRACTS IN CLASSICAL PATHWAY OF COMPLEMENT SYSTEM

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Introduction: Complement system (CS) is part of the innate immune system and one of the main effector mechanisms of humoral immunity, and its activation could result in autoimmune diseases and chronic inflammation. In this context, the discovery of substances with the ability to modulate the CS activation is of extreme importance for the treatment of inflammatory and autoimmune diseases. So, the aim of this study was to evaluate the in vitro immunomodulatory activity of Musa x paradisiaca extracts in the classical pathway (CP) of CS. Methods: Different concentrations (28-1000 µg/mL) of previously characterized hydroethanolic extracts of M. x paradisiaca bracts (EEB) and flowers (EEF) were evaluated by the hemolytic CS fixation assay. Human serum was used as a source of complement (ethical approval: CEP HC-UFPR n° 1.703.531). The results obtained were expressed in relation to the percentage inhibition of hemolysis and compared with the control heparin by ANOVA and Tukey’s test Results and discussion: EEF inhibited hemolysis significantly at concentrations of 562.3 and 1000 µg/mL when compared to heparin, which is an inhibitor of SC activation. On the other hand, the EEB showed significant inhibition from 158.1 µg/mL, which allows to infer that this extract has a better activity in the inhibition of the CP of CS compared to the EEF. Conclusions: These data suggest that extracts of M. x paradisiaca have in vitro anti-inflammatory potential and may be promising for the treatment of inflammatory diseases that have their course related to CS activation.

Acknowledgments: CAPES, SETI Paraná.
OPHTALMIC APPLICATION AND EVALUATION OF COROSOLIC ACID TOXICITY

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Introduction: Corosolic acid (CA) is a natural pentacyclic triterpene occurring in a variety of medicinal plants and exhibits numerous biological properties, such as: antiangiogenic, antidiabetic, antioxidative, antiinflammatory and antiproliferative activities. This study aimed to investigate the ophthalmic application of CA, evaluating the citotoxicity and the safety of intravitreal administration of CA using in vitro and in vivo models. Methods: Cytotoxicity effect of CA was evaluated in ARPE-19 cells by sulforhodamine B colorimetric method. An amount of 0.01 mL of CA formulations at 5, 10 and 25 µM was injected in the right eyes of Wistar rats and the contralateral eyes received the vehicle to verify the safety of ophthalmic use. Full-field electroretinography (ERG) was applied to evaluate the retinal activity and, therefore, the safety of intravitreal injection of CA. ERG recordings were performed before, 7 and 15 days after the intravitreal injection. Animals were sacrificed on the 15th day and the histological analysis of retina was carried out under light microscopy. Results: CA did not present cytotoxicity for ARPE-19 cells at concentrations below 35.5 µM after 48 hours of treatment. ERG recordings and histological evaluation did not show any signs of retinal toxicity. Conclusions: CA revealed safety for potential ophthalmic use and may be an useful alternative in the therapy of ocular diseases.

Ethical Approval: All experiments were carried out in accordance with the statement of Association for Research in Vision and Ophthalmology (ARVO) for the Use of Animals in Ophthalmic and Vision Research and were approved by the Ethics Committee on Experimental Animals of UFMG (Protocol nº 227/2017).

Acknowledgments: CAPES, CNPq, FAPEMIG.

ID: 473

SAPUCAIA (Lecythis pisonis CAMB.) A RICH NUTRITIONAL SOURCE AND CHARACTERIZATION OF ARILS A NEW CONSUMPTION APPROACH

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Introduction: Lecythis pisonis Cambess, known as Sapucaia, is neotropical native tree from the Amazonian and Atlantic Forest which has been notice for its use as a natural source of nutrients. This study aims to determine the chemical characteristics of the nuts, arils and seed oil of L. pisonis native from Espírito Santo. Methods: The centesimal composition assays and determination of nutritional values were performed using standard methods. The LD₅₀ of the oil was evaluated according to the OECD 423 protocol. Determination of metals Fe, Na and Pb were performed by FAAS. Results and discussion: Lipids (60.14%) and protein (23.33%) were the major nut components. The high ash content suggested significant amounts of minerals in the nuts. The arils had a carbohydrate content of 83.9% and a nutritional value of 363.3 kcal.100g⁻¹. The good quality of oil was suggested by low acidity (0.4 mg NaOH.g⁻¹), low iodine content (93.0 g I₂.100g⁻¹), peroxide index of 2.9 mEq.kg⁻¹, saponification index of 182.66mg KOH.g⁻¹ and a higher concentration of mono-unsaturated than poly-unsaturated fatty acids. The oil was also classified by GHS as Category 4 and by OECD as having low toxicity (LD₅₀>5000 mg.kg⁻¹ in mice and 405 mg.kg⁻¹ in humans). Lead was not detected in any sample. Iron was detected in nuts (2.17±0.47 mg.100g⁻¹), aril (1.12±0.15 mg.100g⁻¹) and oil (9.40±0.005 µg.g⁻¹). As sodium at 3.27±0+62 mg.100g⁻¹ in nuts, 6.62±1.06 mg.100g⁻¹ in the aril and 0.7±0+22 µg.g⁻¹ in oil. Conclusions: Thus, consumption of oil, nuts and arils should be recommended as an excellent nutritional source.

Ethical approval: The study was approved by the Ethics, Bioethics and Animal Welfare Committee of UVV under the number CEUA-UVV 338/2014.

Financial Support and acknowledgement: FAPES (TO # 241/2016) e SEAG/FAPES (TO # 665/2016). CNPq (#308631/2016-1 PQ and # 310680/2016-6 PQ).
Section
Pharmaceutical and Cosmetic Technology
AMPHOTERICIN B-LOADED POLY(Ɛ-CAPROLACTONE) (PCL) NANOFIBERS: AN ALTERNATIVE THERAPY SCHEME FOR LOCAL TREATMENT OF FUNGAL ENDOPHTHALMITIS

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Introduction: Fungal endophthalmitis (FE) is a complex pathology characterized by eye’s infection and inflammation. The treatment of fungal endophthalmitis is based on surgery, intraocular injections and systemic medication. However, the improvement of conventional therapy is mandatory. In this study, amphotericin B-loaded PCL nanofibers (AmB PCL nanofibers) were developed as an alternative therapy scheme for local treatment of FE.

Methods: AmB PCL nanofibers were developed by electrospinning technique. AmB PCL nanofibers were characterized by SEM and FTIR. In vitro AmB release from PCL nanofibers as well as the capability of AmB to inhibit Candida species were studied. In vitro ocular biocompatibility was evaluated by analyzing the viability and morphology of ARPE-19 cells in direct contact with the AmB released from PCL nanofibers.

Results and discussion: AmB PCL nanofibers were successfully produced by electrospinning technique. SEM images revealed the interconnectivity, porosity and the random orientation of nanofibers. FTIR results indicated the absence of chemical interactions between drug and polymer. During 10 days, AmB was controlled released from PCL nanofibers; and it was capable of inhibiting Candida species. ARPE-19 cells showed normal morphology in contact with AmB; and 98% of these cells showed viability.

Conclusion: AmB was incorporated into the polymeric chains and they apparently did not interact chemically. The preserved AmB was controlled released from PCL nanofibers in therapeutic dosages, which were essential to eliminate Candida species in vitro. AmB did not affect the integrity of APRE-19 cells. Finally, AmB-loaded PCL nanofibers represent an alternative therapy scheme for local treatment of FE.

Financial Support: The authors wish to thank the CNPq/MCT (Brazil), FAPEMIG (Brazil – Grants APQ–01522–16), Federal University of Ouro Preto (UFOP) and Federal University of São João del-Rei (UFSJ) for the financial support.

DEVELOPMENT OF SUNSCREENS FORMULATIONS CONTAINING NATURAL ACTIVES INGREDIENTS: A QUALITY BY DESIGN APPROACH

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Skin cancer is the most common type of cancer and has become a public health concern in worldwide. The most effective preventive action is the photoprotection, including the use of sunscreens. Many studies support the topical use of natural actives because of their antioxidant efficacy, but few studies show an improvement of the photoprotective efficacy in terms of sun protection factor (SPF). Therefore, investigations aiming the study of the efficacy of sunscreens containing these actives are important. Quality by Design (QbD) is a systematic approach for pharmaceutical product development. Design of Experiments (DoE) is a toll of this approach that helps to reach goals with a smaller number of tests and greater accuracy avoiding wasting resources. Aiming to determine the most promisor natural active within resveratrol, olive leaf and Polypodium leucotomos extracts for the development of a multifunctional sunscreen product, we developed and investigated the in vitro SPF of different formulations, using the QbD approach. JMP11 software was used for the DoE analysis, which were carried out in two phases: screening and optimization. At the first, variables were investigated in a wide range and combinations. For optimization, the investigation focused on the maximum response actives and ranges. DoE showed to be an effective tool for the screening. A predictive model was built with Rsquare = 0.907. Resveratrol and Olive leaf extract showed the most significant effect in SPF values (p < 0.0005). The Polypodium leucotomos extract investigated do not influenced significantly on SPF of the formulations (p = 0.7733).
DEVELOPMENT AND CHARACTERIZATION OF MESOPOROUS SILICA NANOPARTICLES (MSN) FOR DENTAL CARIES PREVENTION

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Dental caries is one of the most prevalent diseases in the world and represents a major public health problem in some countries. In this context, the use of nanometric systems as carriers of caries preventive agents, such as fluoride, is shown as a promising therapeutic alternative. Among the alternatives available in the nanotechnology field, the use of mesoporous silica nanoparticles (MSN) for this purpose can be highlighted. Thus, the objective of this study is to develop and characterize five different MSNs containing fluoride and / or calcium and to evaluate its efficacy and safety in order to prevent the development of dental caries. The MSNs were obtained through the nanoprecipitation technique, varying the molar ratio of water / tetraethylorthosilicate (TEOS), NH₃/TEOS and amount of hexadecyltrimethylammonium bromide (CTAB), lyophilized and physicochemically characterized. The determination of fluoride in MSN was performed by ion chromatography (IC) with conductimetric detection and presented 9.3 ± 0.1% [w/w] of medium content. The determination of calcium was performed by inductively coupled plasma optical emission spectrometry (ICP-OES) and presented 10.7 ± 0.8% [w / w] of medium content. The results indicated that the proposed method for the development of MSN is viable, since MSN had a mean diameter of 183.18 ± 1.5 nm and a polydispersion index (PdI) of 0.240 ± 0.021, using the scattering technique (DLS) and zeta potential of - 29.66 ± 0.18 mV. In addition, the formed MSN presented spherical shape through the technique of transmission electron microscopy (TEM). It was possible to develop MSNs that provide fluoride and calcium to the dental structure satisfactorily.

Acknowledgments: CAPES, FAPERJ and CETEM

DEVELOPMENT OF INTRAOCULAR MICRO IMPLANTS INTENDED FOR THE TREATMENT OF OCULAR TOXOPLASMA

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Introduction: Ocular Toxoplasmosis is a clinical pathology characterized by retina/choroid inflammation, being the main cause of posterior infectious uveitis in the world. Objective: To develop poly (lactic acid-co-glycolic acid) (PLGA) and spiramycin intraocular micro implants for the treatment of Ocular Toxoplasmosis disease. Methods: Solutions were prepared using different concentrations of PLGA and spiramycin. Micro implants were characterized by Fourier transform infrared spectroscopy (FTIR), thermogravimetric (TGA) and differential scanning calorimetry (DSC). Morphological analysis was done using scanning electron microscopy (SEM). Spiramycin quantification method was previously validated using spectrophotometry. In vitro release study was performed according to the sink conditions. In vitro biocompatibility study was performed using ARPE-19 and evaluating cytotoxicity according to the reduction of tetrazolium salt (MTT). Results and discussion: Cylindrical implants were obtained. FTIR spectra demonstrated preservation of the absorption bands typical of PLGA's and spiramycin after incorporation of this drug into the polymer matrices. TGA and DSC showed the disappearance of spiramycin characteristic peak due to drug molecular dispersion within the polymer matrix. The developed spectrometric method was validated. Drug distribution in the micro-implants presented expected contents. Through SEM analysis, it was possible to verify the influence of polymeric morphology devices on the spiramycin release. Micro-implants allowed drug controlled release. Cytotoxicity results showed spiramycin and polymers used were not toxic to the cells. Conclusion: There are no micro-implants in the pharmaceutical market that contain approved and available anti-toxoplasmosis drugs, which highlights these systems as an alternative for its treatment.
EXTRACELLULAR EXPRESSION OF RECOMBINANT L-ASPARTAGINASE II FROM *Saccharomyces cerevisiae* IN *Pichia pastoris* WITH HUMANIZED GLYCOSYLATION

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Introduction: L-asparaginase is an efficient inhibitor of tumor growth, used in chemotherapy sessions against acute lymphoblastic leukemia (ALL) tumor cell with 80% total recovery of treated patients. The high production costs of L-asparaginase and the low international demand for the native enzyme of *Escherichia coli* resulted in the interruption of its trade in the Brazilian market, which is dependent on its importation. The severe immunogenic effects of treatment with the *E. coli*’s enzyme led us to seek other sources of L-asparaginase, among them *Saccharomyces cerevisiae* and *Pichia pastoris*, the latter with great potential for extracellular expression, which would decrease the cost of production. The proteins expressed by these microorganisms present hyperglycosylation, especially *S. cerevisiae*, resulting in an immunogenic effect. Objective: Aiming to overcome these drawbacks, we propose cloning and expressing *S. cerevisiae*’s L-asparaginase II fused with heterologous extracellular expression signaling in *P. pastoris* GlycoSwitch pep4- sub2-, a strain of *P. pastoris* protease knockout that presents humanized glycosylation. Metodology: For this, we used the circular polymerase extension cloning technique to build two different vectors, with two different signaling sequence, both fused with L-asparaginase II. Linearized vector was transformed in *P. pastoris* GlycoSwitch pep4- sub2- and the enzyme was expressed by inducing the AOX1 promoter with methanol. The enzyme was analyzed in with SDS-PAGE electrophoresis and the asparaginase activity measured by hydroxylamine. Results: The *P. pastoris* strain was successfully transformed and L-asparaginase II fused with the signaling sequence was incorporated into genome. The extracellular medium presented asparaginase activity and the SDS-PAGE revealed a protein with approximately 45kDa, similar to native L-asparaginase II, although the protein expressed is theoretically glycosylated. Biochemical structure will be characterized. Financial support: This work is supported by CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) and FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo), grant (Projeto Temático) 2013/08617-7.

ANTIOXIDANT AND PHOTOPROTECTIVE ACTIVITY OF OLIVE LEAF EXTRACT IN SUNSCREENS

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Skin cancer is the most common type of cancer and represents an important public health problem, mainly in countries as Brazil with high levels of UV radiation. Photoprotection is an important strategy for skin cancer and photoaging prevention. Investigations focused on the development of sunscreen formulations with improved efficacy and safety are valuable for these prevention. Plant extracts are important agents for photoprotection due its composition. Olive leaf extract presents a significant amount of phenolic compounds, such as oleuropein. The present study aimed to investigate the antioxidant and photoprotective activities of olive leaf extract for the use in sunscreens. DPPH antioxidant activity and UV absorption spectrum of olive leaf extract were evaluated. Gel-based and sunscreen formulations were developed with and without extract and their sunscreen protection factor (SPF) in vitro were determined. Stability and organoleptic characteristics of the formulations developed were evaluated. Olive leaf extract showed high antioxidant activity compared to resveratrol (an phenolic compound well known due its higher antioxidant capacity) and an UV broad spectrum absorption (UVA and UVB). Broad spectrum sunscreen formulations were developed with SPF higher than 15, UVA/UVB ratio and critical wavelength higher than 0,33 and 370 nm, respectively. The gel-based formulation with olive leaf extract did not show a significant SPF value. However, a synergistic effect of the Olive leaf extract combined with UV filters in sunscreen formulations was observed, showing a significant increase in SPF values using different concentrations of the extract. Sunscreen formulations were stable and presented satisfactory organoleptic characteristics.
MICROFLUIDIZED LIPOSOMES AS CRISPR/CAS9 VECTORS AIMING TO MPS I MICE GENE EDITING

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Introduction: Mucopolysaccharidosis type I (MPS I) is caused by deficiency of α-L-iduronidase (IDUA), which results in systemic accumulation of glycosaminoglycans (GAG), leading to widespread symptoms and impaired quality of life. Currently available treatments have limitations, thus new therapy approaches are needed. The CRISPR/Cas9 system enables precise gene editing and studies have shown the potential of lipid carriers as nonviral delivery systems for gene therapy. Methods: A liposomal vector was prepared by hydration of a thin lipid film followed by microfluidization, complexed with the CRISPR/Cas9 plasmid, characterized, and delivered either via intravenous or nasal route aiming to correct MPS I mice through the insertion of a corrective murine Idua gene at the ROSA26 “safe harbor” locus. Results and discussion: The experimental conditions used yielded positively-charged monodispersed liposomal complexes exhibiting a mean size close to 120 nm. DNA was strongly complexed with nanostructures, allowing the protection against enzymatic degradation. Newborn intravenous treatment (n= 6 MPS I mice, ethics committee CEUA/HCPA#150416) resulted in 6-month sustained serum IDUA activity levels (5-7% of normal activity). After six months there was a significant increase in tissue IDUA activity, especially in the heart and lungs (over 10% of normal levels), but also in liver and kidneys, at levels sufficient for clearance of at least half of GAG accumulation in all analyzed organs, but the brain. On the other hand, nasal administration in adult MPS I mice significantly increased IDUA enzyme levels in all brain areas. Furthermore, it resulted in secretion of active enzyme to the plasma and efficient uptake by other tissues as heart and lungs. Conclusions: The overall data provided proof-of-concept for lipossomal CRISPR/Cas9 complexes targeting of the ROSA26 locus in vivo aiming to express therapeutic amounts of IDUA for the potential treatment of the widespread and cognitive symptoms of MPS I.

Financial support: FIPE-HCPA, CNPq Brazil

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USING DESIGN OF EXPERIMENT THE PRE-FORMULATION PHASE OF NANOEMULSIONS: UNDERSTANDING THE EFFECT OF THE EXCIPIENTS ON DROPLET SIZE

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The essential oil extracted from Rosmarinus officinalis (Ro) has some pharmacological properties, such as antimicrobial activity, antioxidant and antineoplastic activity. However, the development of a pharmaceutical formulation from this source is a challenging process due to its complex chemical composition. Therefore, the use of Design of Experiment methodologies (DoE) seems to be an interesting approach, allowing a systematic evaluation of each factor under investigation as well as the effect of their interactions. Thus, the aim of this study was to apply a 2³ full factorial design, with 4 central points, to develop and characterize the effect of HLB (10, 13 e 16), oil phase (1, 3 e 5%) and surfactant (3, 7.5 e 12%) on the average droplet size and polydispersity index (PDI) of nanoemulsion prepared with essential oil from Ro using acoustic cavitation. The results revealed that all formulations had a monodisperse distribution (PDI < 0.2) and the interaction between HLB-Surfactant decreased the droplet size, likely due to the synergic effect of decrease interfacial tension and approximation of the required HLB of the oil (16.5). On the other hand, at oil level 5% the droplet size increased with the increment of surfactant, suggesting the optimal concentration of surfactant to minimize the droplet size is close to 3%. The use of DoE enabled to understand the role of HLB, amount of oil phase, surfactant and set these parameters to minimize the droplet size of nanoemulsions prepared with essential oil from Ro intended to pharmaceutical use.

ID: 24
PREPARATION AND CHARACTERIZATION OF MICROSPONGES CONTAINING METHYLENE BLUE USING DIFFERENT ORGANIC PHASES

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Introduction: Drug delivery systems offers several advantages when compared to conventional dosage forms. Among the benefits, it can be mentioned the modulation of the release process, reduction of toxicity, improvement of drug availability into a specific site, which leads to better adherence to treatment by patients. Polymeric microsponges (MS) are rigid and porous structures able to incorporate a relatively large amounts of drug into their interconnect channels. MS constitute a relatively new strategy, thus has a few studies using them. Therefore, the aim of this work was to obtain and characterize MS developed with different organic solvent proportions and containing methylene blue (MB) as a model drug. Methods: MS was prepared by quasi-emulsion technique. A dispersion of ethylcellulose (0.5%, w/w) and HPMC phthalate (0.03%, w/w) was prepared in dichloromethane (DCM) (100, 80, 70 and 50%, v/v) and ethanol (0, 20, 30 and 50%, V/V) (organic phase), being denominated M10, M8, M7 and M5, respectively. Aqueous solution (1%, w/v) of porogenic agent and MB (0.25%, w/w) was dispersed in polymeric solution. This dispersion was dripped into an aqueous poloxamer 188 dispersion (aqueous phase) and remained in magnetically stirring for 24 h. MS were dried at 60 °C in the hot air oven and they were evaluated as morphology by SEM, product yield (PY), drug content (DC), entrapment efficiency (EE) and particle size (PS) by dynamic light scattering (DLS). Results and discussion: All MS displayed spherical morphology, smooth surface and uniformly porous structures. MS prepared at concentrations higher than 80% of DCM showed more spherical morphology and more homogenous size. Moreover, the increase of DCM from 50 to 100% reduced the size from 7.44 to 2.57 µm. PY values were 52.79, 49.59, 48.21 and 44.82%, EE was 41.35, 25.12, 18.01 and 10.78%, and DC was 0.10, 0.06, 0.04 and 0.02% to M5, M7, M8 and M10, respectively. Conclusion: Therefore, it was possible to prepare MS with different organic solvent proportions containing a hydrophilic drug, but the better results were obtained using the same amount of dichloromethane and ethanol.

Acknowledgments: CAPES, CNPq, Finep and PPG/UEM.

DEVELOPMENT OF ITRACONAZOLE NANOCARRIERS AS A NEW STRATEGY TO IMPROVE CUTANEOUS LOCALIZATION IN THE TREATMENT OF FUNGAL INFECTIONS

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Introduction: This study aimed at developing nanostructured lipid carriers (NLC) for topical delivery of itraconazole, aiming the improvement of cutaneous drug localization in the treatment of human and veterinary sporotrichosis lesions. Methods: The nanocarriers were developed combining solid (glyceryl behenate) and liquid (tricaprylin) lipids at ratios ranging from 7:3 to 3:7 (w/w), surfactants and water. They were characterized for size, morphology and zeta potential. Itraconazole was added at final concentrations of 1-5% (w/w). Transepidermal water loss was measured as an index of tissue permeability after skin treatment with nanoparticles or water (control) for 24 h; as model tissue, we employed intact porcine skin or skin damaged with a linear incision to mimic a wound. Results: Ratios of solid:liquid lipid of 5:5 and higher resulted in nanoparticles with diameter smaller than 230 nm (polidispersity index). Acknowledgments: this study was supported by FAPESP (2013/16617-7). It was considered exempt form IACUC approval.
FLOW BEHAVIOR OF BIOADHESIVE THERMORESPONSIVE POLYMERIC SYSTEMS CONTAINING POLOXAMER 407 AND HYDROXYPROPYLMETHYLCELULLOSE

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Introduction: The investigation of continuous shear (flow) behavior of polymeric systems helps to select better platforms as drug delivery systems for clinical use. The present work describes continuous shear rheometry of bioadhesive thermostressive systems containing poloxamer 407 (Polox407) and hydroxymethylpropylecelulullose (HPMC), as pharmaceutical systems. Methods: Binary polymeric systems were prepared containing Polox407 (15, 17.5 or 20%, w/w) and HPMC (2, 3, or 4%, w/w). Flow rheometry was performed using a MARS II (Haake®) controlled stress rheometer, in flow mode, at 5, 25 and 37 ± 0.1 ºC. The curves were obtained over shear rates ranged from 0 to 2000 s⁻¹, increasing and decreasing over a period of 150 s and keeping at the high limit for 10 s. The flow upcurves were modelled using Ostwald-de-Waele (Power Law) model. Herschel-Buckley model was used to evaluate the yield stress, and the hysteresis area was determined by RheoWin 4.10.0000 (Haake®) software. In each case, at least three replicates were evaluated. Results and discussion: All binary polymeric systems demonstrated shear-thinning behavior at the three temperatures. The systems were pseudoplastic at 5 ºC, whereas at 25 and 37 ºC, they showed plastic behavior (with yield value). The increase of temperature and, Polox407 and HPMC concentration was followed by the increase of consistency index and decrease of flow behavior index. All studied systems were thixotropic at 5 ºC. However, many systems demonstrated rheopetic properties at 25 and 37 ºC, except formulations containing 17.5 % (w/w) Polox407 at 37 ºC, and binary systems with 20% (w/w) Polox407 at 25 and 37 ºC, which displayed thixotropic behavior. Conclusions: All formulations demonstrated shear-thinning behavior, with or without yield value, as well as with higher or lower hysteresis area. These characteristics were consequence of the polymer concentration and temperature of analysis. Formulations with polymeric concentration greater than 17.5% (w/w) Polox407 and 3% (w/w) HPMC demonstrated better flow behavior to be used as drug delivery systems.

Financial support: CAPES, CNPq, Fundação Araucária, and FINEP.

EVALUATION OF CRYOPROTECTANTS IN THE FREEZE-DRYING OF POLYMERIC NANOPARTICLES

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Introduction: The freeze-drying has been considered a great technique for improve the long-term stability of colloidal nanoparticles. The utilization of cryoprotectants decrease the aggregation of nanoparticles, which is due to stress during the process of freeze-drying. The objective of this work was to analyze the influence of cryoprotectants on the lyophilization of nanoparticles. Methods: In this study was used three cryoprotectants (mannose, sorbitol e trehalose) in different concentrations(2,5%,5% and 10%). The sample were previously frozen until -60°C. Then, the samples were submitted to lyophilization for 24 hours. The macroscopic aspect was analyzed. The stability of the particles was analyzed through the zeta potential, particle size and polydispersity index. The Fourier transform infrared (FT-IR) spectroscopy was obtained in the attenuated total reflectance (ATR), the x-ray diffraction (XRD) peaks of the nanoparticles were analyzed with angle of 2θ and scan from 5° to 70°. Results and discussion: the macroscopic aspects revealed that the samples containing 10% of the cryoprotectants more frequently collapsed, and only the samples 5% and 10% of trehalose exhibited a aspect of powder. The stability is in agreement with that reported in the literature, but the samples that presented better stability were those containing sorbitol and trehalose, showing the same particle size before and after the lyophilization. The curves of FTIR presented characteristic peaks of the polymer and the cryoprotectants, demonstrating that lyophilization and addition of cryoprotectants do not induce the formation of new chemical bonds that may interfere with the potential of the drug. The XRD revealed that only the formulations containing trehalose presented crystallinity peaks, however, these peaks are most accentuated in trehalose of 10%. Conclusion: The results presented in the analyses suggest that the cryoprotectants sorbitol and trehalose were the ones that presented a better stability in the formulation, which the concentration of 5% is suggested as the best to be applied to carry out the next experiments.
ENCAPSULATION EFFICIENCY OF A HYDROPHOBIC DRUG IN PLA NANOPARTICLES BY USING TWO METHODS OF PREPARATION

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Introduction: The methods of preparation of the nanoparticles influence the entrapment of the drug in the nanoparticles. The AMTAC-01 (spiro-acridine derivate) presents low bioavailability in biological mediums. The aim of this study was evaluating the encapsulation efficiency of AMTAC-01 in PLA nanoparticles (nanospheres and nanocapsules) front two methods: nanoprecipitation and emulsification solvent evaporation by simple emulsion (O/W).

Methods: The nanospheres were obtained dissolving the Polymer and drug in dichloromethane, this organic solution was sonicated in an aqueous solution containing polyvinyl alcohol (PVA 2% p/v) in sonicator. The nanocapsules were obtained after injection of an organic solution containing the polymer, drug, caprylic capric triglycerides (Mygliol® 812) and soybean phospholipids (Lipoid®) in the aqueous solution containing poloxamer 188 (Pluronic F-68 * 1% p/v). The encapsulation efficiency (EE%) was analyzed by the indirect method with quantification of the free drug fraction present in the supernatant.

Results and discussion: The nanocapsules and nanospheres presented EE of 50.1 % and 84.5%, respectively. The nanosphere showed higher EE. The nanocapsules obtained less EE%, this fact may be related to an intermediate solubility of AMTAC 01 in acetone. However, the EE depends on physical and chemical properties of encapsulating polymers, solvent systems, polymer–drug interactions, and properties of the continuous phase.

Conclusion: The methods of preparation were satisfactory for AMTAC-01 encapsulation with differences in the encapsulation efficiency.

Financial support: CNPq universal (446274/2014)

Acknowledgments: CAPES and CNPq

TECHNOLOGICAL DEVELOPMENT OF POLYMERIC NANOCAPSULES CONTAINING AMYRIN OR AMYRONE

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Introduction: Amyrin is a triterpene isolated from Protium heptaphyllum, highly found in the Amazonia. Amyrone can be synthesized from amyрин. Their anti-inflammatory activities have been highlighted. However, they are lipophilic molecules which limits their formulation in dosage forms. Therefore, the aim of this study was to formulate them as aqueous dispersion by means of their encapsulation in polymeric nanocapsules. Methods: Nanocapsules containing were prepared by the interfacial deposition of a preformed polymer, using poly-epsilon-caprolactone as polymer. Furthermore, chitosan-coated nanocapsules were prepared. Size distribution profiles were determined by laser diffraction and dynamic light scattering. Zeta potential was measured by electrophoretic mobility. All samples were prepared and analyzed in triplicate. Results and discussion: All formulations showed monomodal particle size distribution. Uncoated nanocapsules had mean size of 178±6 nm and 159±7 nm for amyrin- and amyrin-loaded nanocapsules, respectively. However, a slightly increase in the mean particle size was observed for them after the chitosan coating (189±4 nm and 210±8 nm, respectively). Uncoated formulations had negative zeta potential (-10 to -12 mV), whereas the chitosan-coated nanocapsules showed a positive zeta potential (+13 to +30 mV), explained be the cationic properties of the chitosan. Conclusions: Encapsulation of amyrin and amyrone in polymeric nanocapsules was a successfully approach to formulate them as aqueous dispersions. These formulations showed suitable nanotechnological properties, regardless of the nanocapsules coating by chitosan. Their in vivo performance in an anti-inflammatory model will be evaluated in future studies.

Financial support: CAPES/PRO-AMAZONIA; FAPERGS, RSO thanks CNPq for her scholarship (PIBIC/CNPq/UFRGS).
MECHANISMS OF INTERACTION OF POLYESTER NANOCAPSULES WITH NON-PHAGOCYTIC CELLS IN SERUM MEDIUM

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Introduction: Biodegradable polyester nanoparticles provide drug nanocarriers with exceptional properties. This study evaluates the effect of the polyester hydrophilicity on the cytotoxicity of vesicular oily core nanocapsules (NC), prepared from poly-(ε-caprolactone, poly-D,L-lactide, poly-(D,L-lactide-co-glycolide) and poly-D,L-lactide-block-polyethylene glycol and investigates the mechanism of interaction of the NC with three non-phagocytic cell lines. Methods: The viability of Vero, Caco-2 and HepG2 cells incubated with NC was assayed (MTT assay). The NC were labeled with Dil fluorescent dye and fully characterized in media containing fetal bovine serum. Cells were exposed to endocytosis inhibitors (chlorpromazine, cytochalasin D and metyl-beta-cyclodextrin), incubated with NC and the cell-associated fluorescence was quantified by spectrofluorometry. Results and discussion: Nanometric sizes (around 140 nm) and dye loading were stable in culture medium containing serum. Cytotoxicity thresholds of NC were above 100 μg/mL and depended on the polyester composition. HepG2 presented 1.5-2-fold higher endocytic capacity than Caco-2 and Vero cells. The NC were mostly internalized via caveolin-mediated endocytosis in HepG2 and Vero cells, and macropinocytosis in Caco-2 cells. Conclusions: The relatively high IC₅₀ obtained for all polyester NC tested here supports further translation towards pre-clinical and clinical applications. Polymer hydrophobicity had an effect on HepG2 and Vero and less on Caco-2 cells. The levels of NC association and endocytosis mechanisms differed between cell lines tested. Acknowledgements: the authors thank INCT-NANOFARMA (CAPES #2014/50928-2), FAPEMIG (APQ-02864-16), CNPq (310463/2015-7) and UFOP, Brazil, for financial support.

OSCILLATORY RHEOMETRY OF POLYMERIC SYSTEMS CONTAINING POLOXAMER 407 AND HYDROXYPROPRYL METHYLCELULOSE

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Introduction: The association of thermoresponsive and bioadhesive polymers can improve the biomedical application of new drug delivery systems. Thus, the present work demonstrates the oscillatory rheological properties of bioadhesive thermoresponsive systems containing poloxamer 407 (Polox407) and hydroxypropylmethylcellulose (HPMC), to be used as potential pharmaceutical systems. Methods: Binary polymeric systems were prepared containing Polox407 (15, 17.5 or 20%, w/w) and HPMC (2, 3, or 4%, w/w). Firstly, the linear viscoelastic region was determined, and frequency sweep analysis was evaluated from 0.1 to 10.0 Hz. Afterwards, oscillatory rheometry was performed using a MARS II (Haake®) controlled stress rheometer, in oscillatory mode, at 5, 25 and 37 ± 0.1 °C. The storage modulus (G’), loss modulus (G”), dynamic viscosity (η’), and the loss tangent (tan δ) were calculated using the RheoWin4.10.0000 (Haake®) software. The oscillatory properties of at least three replicates were determined. Results and discussion: All binary polymeric systems showed viscoelastic properties that were oscillatory frequency, temperature and polymer concentration dependent. Therefore, for the most of the systems, the increase of oscillatory frequency was followed by G’ and G” increase, except G” of polymer blends containing 20% (w/w) Polox407 evaluated at 25 and 37 °C. Moreover, the increase of oscillatory frequency decreased η’ and tan δ for the most of the systems. Furthermore, the increase of temperature and polymer concentration increased G’, G”, η’, while tan δ was decreased. In this sense, all formulations containing 15, 17.5 and 20% Polox407, at 25 °C and 37 °C, exhibited G’ higher than G”, being classified as viscoelastic systems, mainly at higher concentrations of HPMC. Conclusions: The viscoelasticity of the formulations were dependent of the composition (Polox407 and HPMC concentration), and the temperature of analysis. It was possible to identify polymeric formulations with viscoelastic behavior which have higher potentialas pharmaceutical systems for drug delivery, demonstrating improved rheological properties. Financial support: CAPES, CNPq, Fundação Araucária, and FINEP.
IN SITU MICROPARTICLE IMPLANT AS AN EFFECTIVE SINGLE-DOSE TREATMENT OF CUTANEOUS LEISHMANIASIS

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Conventional leishmaniasis treatments are given by systemic routes, producing severe generalized toxicity, which is particularly unacceptable in the case of localized cutaneous leishmaniasis (CL). Recently, we showed the promising use of poly(lactic-co-glycolic acid) (PLGA) microparticles loaded with 7.8% of an antileishmanial nitrosylated chalcone (CH8) for effective, safe, local, and single-dose treatment of CL [1]. Here, we proposed to optimize the delivery system by increasing CH8 loading in PLGA-microparticles using spray drying instead of emulsification-solvent evaporation (ESE). Two formulations (18%CH8-PLGA and 18%CH8-PLGA-PVP) were produced with high drug loading (18% CH8), round smooth surface, 8 µM mean diameter. These were packed in the inner core with CH8 crystals, as evidenced by SEM and RAMAN microscopy, and DSC [2]. The particles were tested for efficacy against CL in L. amazonensis GFP-infected BALB/c mice using a single intralesional injection (protocol number CAUAP118). Controls were injected with free CH8 (30 µg) or 10 µL of PBS alone. On day 30 or 60 of infection, animals were sacrificed, the infected ears removed, grinded and assayed by fluorometry for instant determination of parasite loads. We found that all CH8 formulations were effective in controlling parasite growth. 18%CH8-PLGA-PVP was the most effective, reducing parasite loads by 98%, as compared with 79% of free CH8. These findings show that spray-drying allowed higher drug loading than ESE, particularly when PVP was added to the polymeric matrix, promoting a more effective and safer single-dose local treatment of CL.


TEXTURE PROFILE ANALYSIS AND SOFTNESS OF MUCOADHESIVE THERMORESPONSIVE SYSTEMS CONTAINING CURCUMIN

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Introduction: Curcumin (CUR) is well known due to its wide range of pharmacological properties, such as anti-inflammatory, antimicrobial, antirheumatic, antioxidant agent, and anti-cancer. However, CUR displays disadvantages, such as low chemical stability and high hydrophobicity. The development of polymeric systems composed of poloxamer 407 (P407) and Carbopol 974P® (C974P) can provide a new platform for CUR delivery. Therefore, the aim of this study was to prepare and evaluate the mechanical characteristics (texture profile and softness) of polymer blends composed of P407/C974P containing CUR. Methods: Formulations were prepared containing 15% (w/w) P407, 0.25% (w/w) C974P with and in the absence of 0.08% (w/w) CUR. The mechanical properties were analyzed using a TA-TX, plus Texture Analyzer in mode of texture profile analysis at 5, 25, 37 °C, and softness evaluation was performed in compression mode at 37 °C. From the force-time plots, the textural parameters (hardness, compressibility, adhesiveness, elasticity, cohesiveness) and softness were derived. The results of texture profile analysis were statistically evaluated by two-way ANOVA, while the softness results were analyzed by one-way ANOVA, and a level of p < 0.05 was accepted to denote significance. Results and discussion: The CUR presence significantly decreased the hardness and compressibility (p < 0.05). Moreover, the increase of temperature significantly increased the hardness, compressibility, adhesiveness and cohesiveness (p < 0.05). The presence of CUR did not influence the softness of the formulation. Conclusions: The system displayed suitable mechanical properties for the development of new CUR delivery systems.

Financial suport: CAPES, CNPq, FINEP and PPG/UEM.
CARRAGEENAN GUM-BASED HYDROGEL CONTAINING P,P’-METHOXYL-DIPHENYL DISELENIDE NANOCAPSULES: CHARACTERIZATION, PERMEATION STUDIES AND PHARMACOLOGICAL EVALUATION

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Nanocarriers, such as nanocapsules system, can improve actives permeation through inner layers of skin, providing a general therapeutic improvement. The organoselenium compound p,p’-Methoxyl-diphenyl diselenide (OMePhSe)² has anti-inflammatory and antioxidant properties, which are potentiated by its incorporation into polymeric nanocapsules, suggesting its possible application towards skin inflammatory-related conditions. This study showed the development of a topical formulation (hydrogel) containing (OMePhSe)²-loaded poly(ɛ-caprolactone) nanocapsules and its evaluation as an alternative treatment for cutaneous UVB radiation-induced skin damage. The nanocapsules were prepared using the interfacial deposition of preformed polymer technique. Formulations with free compound and blank nanocapsules suspension were also produced. The hydrogel was obtained with carrageenan gum (0.3 g) by direct addition of nanocapsules suspension. All hydrogels had pH around 7.00, drug content close to the theoretical value (2.5 mg/g) and mean diameter in nanometric range. Besides, formulations had non-Newtonian flow with pseudoplastic behavior and suitable spreadability factor. Skin permeation studies (CAEE: 552200016.3.0000.5346) revealed that nano-based hydrogel increased the compound content in dermis layer, supporting the in vivo evaluation (CEUA#6133041217/2017), which demonstrated that the hydrogel containing (OMePhSe)²-loaded-nanocapsules was effective in reducing mice ear edema as well as the inflammatory and oxidative injuries UVB radiation-induced. In conclusion, the results demonstrated the feasibility to prepare a hydrogel by thickening (OMePhSe)² nanocapsules suspension with carrageenan gum. Besides, a superior permeation and an improved pharmacological action were achieved by the compound encapsulation.

QUANTIFICATION OF CALCIUM CARBONATE IN TOOTHPASTE BY THERMOGRAVIMETRIC ANALYSIS

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Introduction: Calcium carbonate is used in cosmetic products, mainly in toothpastes with abrasive function to remove biofilm and dental plaque. To verify the physicochemical quality of these products, it is necessary to characterize and quantify calcium carbonate, with a percentage that varies from zero to 30%. This paper aimed to develop an analytical method to quantify calcium carbonate in toothpastes using thermogravimetric analysis (TGA). Methodology: Calcium carbonate was initially quantified by complexometric titration with EDTA, according to the Brazilian Pharmacopoeia 5th Edition. Subsequently, TGA was conducted under a nitrogen atmosphere at a heating rate of 10 °C min⁻¹ to a temperature of 900 °C. Quantification was based on the specific degradation of calcium carbonate to calcium oxide between 600 and 800 °C, with release of CO₂. At this temperature, organic products are no longer present significantly. The results of the analyses were compared by paired tests. Results and discussion: The comparison of results by complexometric titration and TGA revealed no significant difference between the average values (t calculated: 0.0077 < t tabulated: 1.8595) with a 95% confidence interval. Conclusion: TGA showed to be a simple, fast, and effective alternative method to quantify calcium carbonate in toothpastes and could be easily adopted by industries. Financial support: FAPEMIG - Research Support Foundation of Minas Gerais, Brazil.
DOUBLE MUTANT L-ASPARAGINASE OF *Erwinia chrysanthem* WHICH MAY HAVE MINOR ADVERSE EFFECTS

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The l-asparaginase catalyzes the hydrolysis of asparagine and glutamine and is considered the most important medicine for the treatment of acute lymphoblastic leukemia. Currently, the drug is obtained from two bacteria, *Escherichia coli* and *Erwinia chrysanthemi*. In spite of its effectiveness, the high number of adverse effects (AE) and the periods of shortage of l-asparaginase on the market (since 2013 there is no production or its commercialization in Brazil) compromise the treatment. In this way, the search for alternatives to supply the national demand and with fewer AE becomes necessary. Using the enzyme derived from *Erwinia chrysanthemi* we created a double mutant (DM) for error prone PCR and the protein was expressed in *E. coli* BL21(DE3) with IPTG induction; the purification was done by ion exchange; the specific activities were measured by Nessler’s reagent; the evaluation of the action of proteases was done with incubation of the enzyme in the presence of cathepsin B (CTSB) and asparaginyl endopeptidase (AEP). The DM showed 50% higher asparagine activity than wild-type (WT), indicating that it would be necessary to use smaller amounts of enzyme to obtain the same results as the WT. The glutaminase activity is similar, but with the increase of Asparaginase activity the Glutaminase/Asparaginase ratio is 43% lower, which may reduce some AE caused by the hydrolysis of that amino acid. The protease activity profile of the DM remained the same as the WT, CTSB-sensitive and AEP-resistant. The results show that the enzyme may contribute to the reduction of adverse effects.

Financial support: This work is supported by FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo) 2016/25896-5, grant (thematic project) 2013/08617-7.

DEVELOPMENT OF TUCUMÃ (*Astrocaryum vulgare*) AND BIRUTI (*Mauritia flexuosa*) OILS BASED BIGELS FOR COSMETIC APPLICATIONS

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Introduction: Biphasic systems most known are emulsions, which are thermodynamically unstable liquid dispersions and stabilized by surfactants. One strategy for stabilizing liquid two-phase systems is changing viscosity of both outer and inner phases producing bigel formulations. Bigels are more stable than emulsions, have simplified preparation as gels and are free of surfactants. Bigels present oil phase and show a great moisturizing potential. Moreover there is a lack of scientific information published about these promising formulations. **Methods:** Bigel formulation was based in hydroxyethylcellulose, preservatives, propylene glycol and water for aqueous phase. There were used tucumã or buriti oils and bee wax or precipitated silica as oil phase gelator and antioxidant. Both organogel and hydrogel were prepared separately by mechanical stirring. Then proportions of 10:90, 70:30 and 50:50 of organogel and hydrogel, respectively, were incorporated by mechanical stirring. To evaluate stability centrifugation test was performed. Microscopic structure and phase orientation were determined by optical microscopy using stain. **Results:** All bee wax formulations both containing tucumã and buriti have separated on centrifugation test demonstrating lack of stability. However precipitated silica formulations both containing tucumã and buriti were oil stable only at 10:90. Microscopy of bigels showed a perfect dispersion of the inner phase into the outer phase with a perfect round shape. Both bigels containing buriti and tucumã oils at 10:90 and 70:30 were oil-in-water dispersion, while 50:50 were oil-in-water formulations. **Conclusion:** Further analysis must be done to fully comprehend bigel component interactions and determine which factors influence on stability and phase orientation. **Financial support:** FAPERJ
FENRETINIDE DELIVERY SYSTEM FOR BREAST CANCER CHEMOPREVENTION

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In spite of the high incidence of breast cancer, there are very few pharmacological options for its prevention. Due to its ability to regulate cell growth and differentiation, fenretinide has been considered a promising candidate for chemoprevention. However, its serious systemic adverse effects and high lipophilicity limits its systemic use. To overcome these limitations, we developed a bioreponsive, precursor dispersion containing phosphatidylcholine, triglyceride and water, capable of transitioning into a nanostructured gel upon subcutaneous administration for sustained release of fenretinide locally in the breast tissue. We evaluated the relationship between composition and the type of formed phase using polarized light microscopy, rheological and swelling behavior, and release kinetics in vitro and in vivo using a bioimaging system. The precursor dispersion formed lamellar and hexagonal liquid crystalline gels when added water at 20% and up; swelling followed second order kinetics, and reached a plateau after 48 h when the dispersion was placed in contact with water or a gel that mimics more closely the structure of the subcutaneous tissue. Drug incorporation did not alter phase behavior. Rheology data showed that the precursor formulation displayed Newtonian behavior, while the gel presented pseudoplastic behavior. The gel was formed in vivo within 48 h, and sustained Alexa Fluor 647 release for over 3 weeks. Taken together, these results suggest in vivo formation of the nanostructured gel, which in turn, was capable of sustaining drug release. With this study, we aim to contribute to the development of a more effective, well-accepted and much needed platform for the chemoprevention of breast cancer.

Ethical Approval: CEUA #4906211117;

INTRADUCTAL ADMINISTRATION OF BIOADHESIVE NANOCARRIER IMPROVE CYTOTOXICITY OF PIPLARTINE AND MAMMARY TISSUE TARGETING: A NEW STRATEGY FOR TREATMENT OF IN SITU DUCTAL CARCINOMA

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As a new strategy for the treatment of ductal carcinoma in situ (DCIS), we developed bioadhesive nanocarriers for intraductal administration of chemotherapeutic agent Piplartine. To confer bioadhesiveness, the nanoemulsion (NE) surface was modified with chitosan (NE-Q) or hyaluronic acid (NE-HA). To assess the ability of NE to promote retention in the breast tissue following intraductal administration, a fluorescent dye was encapsulated and an in vivo imaging system (IVIS Spectrum) was used for fluorescence tracking for 1-120 h. The influence of nanocarriers on cell viability of MCF7 and T47D strains was evaluated by MTT by treatment for 48 h. We also evaluated how the cytotoxicity of piplartine is influenced by (i) its nanoencapsulation and (ii) its co-encapsulation with tributyrin and metformin. Diameter of the NEs was below 60 nm, while their zeta potential varied according to the polymer used for surface modification: +10.6 ± 3.0 (NE-Q) and -5.7 ± 1.6 mV (NE-HA). Both NEs were able to remain in the mammary tissue for up to 120 h. Compared to piplartine solution (in DMSO), its encapsulation in NE-HA and NE-Q shifted the cell viability curve, decreasing the concentration required to reduce viability to 50% (IC50) by 2.7-4.0 times depending on the cell line. More marked reductions in drug IC50 in MCF7 cells were observed when co-encapsulating in NE-HA with tributyrin (10.3 fold) and metformin (10 fold). The results demonstrate benefit of the nanocarrier to improve the retention of encapsulated compounds in the mammary tissue and increase the cytotoxic effect of the drug piplartine while allowing the localized treatment.
ASSESSMENT OF CHEMICAL ELEMENTS IN COSMETICS’ EYESHADOWS BY X-RAY FLUORESCENCE AND INTERNATIONAL NOMENCLATURE OF COSMETIC INGREDIENTS CHARACTERIZATION

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Introduction: Cosmetic industry sector grows each year and there are many new products coming to the market with few legal requirements, much less inspections. Therefore, it’s relevant to inquire the cosmetic products quality. In this investigation EDXRF technique was used for inorganic chemical elements determination in solid eyeshadows, which results were compared with product label composition and eyeshadow samples were grouped by elements concentrations and color similarity. Methods: Samples were prepared at 90kPa into 13mm diameter discs for EDXRF. INCI standardized nomenclature was used for labels investigation to obtain data on legal regularity. Data of samples were clustered by similarity, measuring relative concentrations of detected chemical elements. Calculating the correlation among such values, a similarity matrix was used to generate a dendrogram. Results and discussion: Lead was found in silver color-S12E and copper color-S22I samples above permissible limits (20ppm). Same composition was reported for pink (S01A), black (S02A) and brown (S03A) samples, but the same chemical elements were not detected by EDXRF in them. The best correlation, in cluster analysis, was found between samples S08D and S23J (0.961). However, this samples are distinct colors and not belonging to the same manufacturer. The dendrogram analysis showed seven groups of similar samples according to EDXRF data. Relations among six eyeshadows’ colors and chemical compositions were discovered by using decision trees, where the most determinant elements were Mn, S, Cl, Ca and Fe, in this order. Conclusions: Commercial regularization and INCI standardization of eyeshadows in Brazil are not fully complied by the manufacturers of the investigated brands.

Acknowledgements: The authors wish to thank University of Sorocaba (SP, Brazil) for the financial support (process PROBIC nº. 012/2015) and Foundation for Research Support of the State of São Paulo – FAPESP (SP, Brazil) (process nº. 2012/15651-4).

NANOESTRUCTURED SYSTEMS FOR THE CUTANEOUS DELIVERY OF H2S DONOR COMPOUNDS FOR TREATMENT OF PSORIASIS

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Introduction: Psoriasis is a chronic inflammatory disease with significant impact on the quality of life. Corticotherapy is commonly used, but its numerous local and systemic side effects drive new treatment search. A recent endogenous signaling molecule, hydrogen sulfide (H₂S), has been negatively correlated with psoriasis severity, indicating that H₂S-releasing molecules may be of interest to treat psoriasis. Here we developed topical nanocarriers to incorporate a new hybrid drug based on a combination of a H₂S-releasing corticosteroid to potentiate steroid anti-inflammatory effects without needing increased corticosteroid dosage, reducing side-effects. Methods: Several formulations were developed, which were separated in two groups: group A contained phosphatidylcholine (PC), polysorbate, glycerol and oleic acid, while group B contained PC, sunflower oil and Shea butter. The nanocarrier rheological behavior, bioadhesive potential, influence on the cutaneous barrier and ability to deliver the co-drug to the skin were assessed. Results: The type of phase formed varied with water content in both A and B groups, with gel-based lamellar phases observed with water at 20%, and a nanoemulsion stabilized by lamellar phase with water at 70%. The formulations displayed pseudoplastic rheological behavior, and bioadhesive potential ~2-fold higher than water. Formulation A with 20% of water increased transepidermal water loss, indicating disruption of cutaneous barrier function; however, caused acanthosis. The co-drug was stable in all formulations, but only those from group B increased co-drug dermal penetration (1.7-2.6-fold). Conclusion: We conclude that formulations from group B are promising candidates for the new hybrid drug topical delivery.
DEVELOPMENT OF AN ORABASE CONTAINING POMEGRANATE EXTRACT FOR ORAL HYGIENE IN DOGS: PREPARATION, QUALITY EVALUATION AND PRELIMINARY ANTIMICROBIAL \textit{in vitro} ANALYSIS

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**Introduction:** The use of medicinal plants as a therapeutic and prophylactic resource in veterinary dentistry deserves attention. The aim of the present study was to develop an adhesive oral ointment (orabase) containing pomegranate peel extract, intended for use in dogs to contribute to oral hygiene. **Methods:** The extract was obtained from pomegranate peel by maceration and percolation using ethanol as solvent. The alcoholic extract was incorporated in an orabase and the formulations were named ORA (pure base), ORA1 (25% w/w), ORA2 (37.5% w/w) and ORA3 (50% w/w). The formulations were submitted to \textit{in vitro} microbiological tests by disc-diffusion method in Mueller Hinton medium to investigate the sensitivity of microorganisms collected from the oral cavity of 12 Labrador retrievers dogs (Ethic Comitte Approval: 046/2015). Finally, pH, hardness, cohesiveness and adhesiveness were researched from ORA and ORA2. **Results and discussion:** The mean values of inhibition halos diameters (mm±SD) were: 0.0 mm (0.0 mm) for ORA; 29.8 mm (±3.4 mm) for ORA1; 31.5 mm (±3.9 mm) for ORA2; and, 32.6 mm (±4.9 mm) for ORA3. The pH of ORA was 4.14 and addition of the extract promoted a decrease of this value to 2.74 (ORA2). The hardness, cohesiveness and adhesiveness values decreased after incorporation of the extract into the base. **Conclusions:** The formulation containing 37.5% w/w extract presented hardness, cohesiveness and adhesiveness appropriate for use as adhesive bucal ointment and, adequate inhibitory activity \textit{in vitro} against microorganisms from natural microbiome collected from the oral cavity of the dogs under the conditions tested. The results suggests that the product is a viable alternative for use to oral hygiene of dogs. **Acknowledgments:** This research was supported by FAPES and FAP/PRPPG-UFES.

β-CYCLODEXTRIN-COMPLEXED Ocimum basilicum ESSENTIAL OIL FOR USE AS FOOD PRESERVATIVE: OBTENTION AND PHYSICOCHEMICAL EVALUATION

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**Introduction:** Essential oils (EOs) are complex blends of volatile molecules having a great interest by pharmaceutical, cosmetic, agricultural, and food industries. Cyclodextrin inclusion complexes also represent a valid strategy to increase stability and decrease volatility of EOs. In recent years, the application of EOs as natural preservatives for foods has been considered. The aim of this project was to prepare inclusion complexes between β-CD and basil essential oil (BEO) to use as preservative for foods. **Methods:** Initially, BEO components were identified by GC-MS and GC-FID. Inclusion complexes β-CD:BEO (1:1 and 1:2, stoichiometric ratio) were prepared by kneading and lyophilization techniques. Physical mixtures were prepared in the same proportions. Combined methods were used to confirm the complexes formation: scanning electronic microscopy (SEM), thermal analysis (DSC and TG/DTG), X-ray diffraction (XRD) and carbon magnetic nuclear resonance ($^{13}$C NMR). **Results and discussion:** The major componentes of BEO were methyl chavicol (76.20%) and linalool (20.57%). According to the XRD results, it was possible to observe a reduction in crystallinity of the complexes prepared by lyophilization when compared with the diffractiongrams of the pure β-CD, physical mixtures and kneaded complexes. Enlargement of the diffraction peaks and the appearance of new peaks were observed too. The reduction of crystallinity in lyophilized complexes was confirmed by $^{13}$C NMR. These findings confirm the results obtained in the thermal and image analysis. **Conclusions:** Since the characterization techniques are complementary, the analysis of the data set confirms the formation of the complexes prepared by lyophilization, in both proportions studied. **Acknowledgments:** This research was supported by FAPES and FAP/PRPPG-UFES.
EFFECT OF PEQUI OIL CONTENT ON THE PHYSICOCHEMICAL PROPERTIES OF CHITOSAN-BASED COATING-FORMING EMULSIONS FOR OSTEOARTHRITIS TOPICAL TREATMENT

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Introduction: Osteoarthritis is the most common arthritic condition with the incidence and prevalence projected to rise as the elderly proportion of the population increases. An alternative to treating the disease is the inclusion of medicinal plants. Caryocar coriaceum Wittm. fruit pulp fixed oil (CCFO), popularly known as pequi, is important source of food and used in the folk medicine as wound healing, anti-inflammatory and for treatment of diseases of the respiratory tract, rheumatic and muscular pains. In this study, we evaluated the effect of CCFO content on the physicochemical properties of chitosan-based coating-forming emulsions as alternative for osteoarthritis topical treatment. Methods: Coating-forming emulsions were developed based on chitosan (1.5% w/v) and CCFO (0.2% and 0.6%) using rotor stator homogenization. Emulsions were characterized in terms of droplet size, polydispersity index, ζ-potential and rheological behavior. Results and discussion: The results demonstrated that CCFO droplet size significantly affected by the emulsion composition. Emulsion droplet size decreased as the CCFO concentration increased; the smallest size (286 nm) was observed with the CCFO content (0.6%). Emulsion polydispersity was affected by CCFO concentration; the lowest value (0.404) was presented with 0.6% CCFO, indicating higher of dispersion homogeneity. All the emulsions, independently of the CCFO content had positive ζ-potential values. Emulsion rheological behavior and apparent viscosity were not affected with different CCFO concentrations. Conclusions: Emulsions demonstrated pseudoplastic behavior, which is favorable for topical application. Incorporating CCFO in the emulsions with better functional properties could be used as alternative for osteoarthritis treatment.

Acknowledgments: CAPES, CNPq, FINEP and FAPITEC/SE for the financial support and fellowships.

PREPARATION AND PHYSICOCHEMICAL CHARACTERIZATION OF PLA NANOSPHERES CONTAINING A DERIVATE SPIRO-ACRIDINE

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Introduction: The polymeric nanoparticles has attracted the research interest in the last years for encapsulation of molecules and drugs. The spiro-acridine derivate, AMTAC-01, is a candidate for drug that presents anticancer activity. Nevertheless, its high hydrophobicity limits its use in the clinic. This study aimed the preparation and characterization of PLA nanoparticles containing the spiro-acridine AMTAC-01. Methods: The polymer and derivate was dissolved in dichloromethane and this organic solution was emulsified in an aqueous solution containing polyvinyl alcohol (PVA 2% p/v) in sonicator. The particle size was confirmed by photomicrography obtained by scanning electron microscopy (SEM) and Atomic Force Microscopy (AFM) images. The infrared analysis (FT-IR) obtained in the attenuated total reflectance (ATR) and the diffractogram of the nanospheres were obtained by X-ray diffraction (XRD) analysis with 2θ angle and scanning 5° to 70°. Results and discussion: The MEV images revealed that the particles have a size smaller than 200 nm ± 1.71 nm, with spherical shape and smooth surface. The FT-IR curves demonstrated that the encapsulation process does not induce the formation of new chemical bonds. The diffractogram of nanospheres with addition of the drug revealed that after encapsulation the drug may be molecularly dispersed in the polymer matrix due the absence of crystallinity peaks. Conclusion: The results of SEM, FT-IR and XRD analyzes suggest that AMTAC-01 has good compatibility with PLA nanospheres and that this system could be a promising drug carrier of AMTAC-01 for cancer treatment.

Financial support: CNPq
Acknowledgments: CETENE, UFRN, CAPES and CNPq
3,3’-DIINDOLYL METHANE INCORPORATION INTO POLYMERIC NANOCAPSULES IMPROVES ITS ANTINOCICEPTIVE ACTION: IN VIVO BEHAVIORAL STUDIES

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3,3’-Diindolylmethane (DIM) is a bioactive that has anti-inflammatory action, but its antinociceptive activity has not yet been elucidated. However, DIM is water-insoluble and photolabile, which restrains its pharmaceutical use. Polymeric nanocapsules (NCs) can improve drug dissolution profile and biological activities. Hence, this study investigated the antinociceptive effect of free DIM or DIM-loaded NCs, in an inflammatory pain model induced by complete Freund’s adjuvant (CFA), as well as on the hot plate and formalin-induced nociception tests. Male Swiss mice were pre-treated with the NCs or free DIM by intragastric route at a dose of 10 mg/kg. After 0.5-8h, the behavioral tests were performed. For the CFA test, the induction was performed by subcutaneous CFA injection. After 24h, mouse mechanical hypernociception was measured using the Von Frey Hair test. For the hot plate test, the animals were individually placed onto a hot plate surface (55±1°C) and the time until the nociceptive response occurrence was recorded. The formalin-induced nociception test was performed by the intraplantar injection of formalin solution, followed by the observation of the licking time over 0–5 min and 15–30 min (neurogenic and inflammatory phases, CEUA#4428090217. Both DIM forms reduced the hypernociception induced by CFA and licking time of both neurogenic and inflammatory phases of pain as well as increased paw withdrawal latency. However, the NCs could prolong those effects (up to 8h), which demonstrated that the nanoencapsulation provided an increase in the pharmacological action of DIM. This study demonstrated that the NCs improved DIM antinociceptive action in mice.

DEVELOPMENT OF BIGELS CONTAINING VEGETABLE OILS FOR COSMETIC APPLICATIONS

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Introduction: Biphasic systems such as emulsions are used in various industrial fields due to the presence of two phases, however these formulations are thermodynamically unstable. In order to stabilize these systems, the viscosity of the outer and inner phases is modified, producing the bigels. Bigels are semi-solid formulations prepared by mixing two gels at a high shear rate. Bigels have advantages such as absence of toxicity related to surfactants, possible delivery of lipophilic and hydrophilic drugs and the presence of the oil phase, transforming the bigel into a formulation with skin hydrating potential. Objective: Develop bigels containing Tucumã (Astrocaryum vulgare) and Pracaxi (Pentachletra macroloba) oils and to evaluate the physical-chemical characteristics and their potential use as cosmetic. Method: Eleven formulations containing hydroxyethylcellulose, Emulfree R and oil were prepared at concentrations ranging in (1.5-3.0% w/w) hydroxyethylcellulose and (2.0-6.0% w/w) oil. Results: The bigels presented desirable organoleptic characteristics, with a slightly yellowish, homogeneous coloring and characteristic odor of the oils. After 24th the stability test was performed by centrifugation, where 1 is being divided of phases and 10 were stable. About pH, it had results of 6.11 ± 0.26. Optical microscopy showed the biphasic structure of the bigel, with an internally rounded and homogeneously dispersed phase. Conclusion: The formulations of bigel were obtained and characterized, and it is still necessary to evaluate their cosmetic applications through in vitro occlusion test, in vivo skin hydration test, and sensory evaluation, besides statistical analysis.
DEVELOPMENT AND IN VIVO PERFORMANCE OF REDISPERSIBLE FLUIDIZED BED GRANULES CONTAINING PHENYTOIN-LOADED NANOCAPSULES

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Introduction: Fluid bed can be used to produce granules with good flowability properties and to improve drug solubility, and therefore its bioavailability. The aim of this study was to produce fluidized bed granules containing phenytoin-loaded nanocapsules (FB-PHT-LNC), studying their flow properties and nanometric characteristics after reconstitution in water as well as their in vivo anticonvulsivant effect.

Methods: The granules were produced in a fluid bed equipment (MiniGlatt, Glatt, Switzerland), using a mixture of maltodextrin and phenytoin as substrate, and nanocapsule suspension or water as binder. Granules containing non-encapsulated phenytoin (FB-PHT) were also prepared. The granules were characterized by cohesion and caking tests on texture analyzer (TA.XTplus, Stable Micro Systems), and after reconstitution in water their particle size distribution (laser diffraction), drug content (HPLC method), pH, and anticonvulsivant effect in a pilocarpine-induced seizures model (n=5) were evaluated.

Results and discussion: Granules FB-PHT-LNC and FB-PHT showed a cohesive nature, regardless of the binder (nanocapsules or water). However, FB-PHT had highest cake strength, and hence great powder segregation potential, while FB-PHT-LNC did not form a cake. The redispersed granules had mean particle size of 0.88 ± 0.05 µm and 25 ± 9 µm and pH of 4.72 ± 0.05 and 5.14 ± 0.10 for FB-PHT-LNC and FB-PHT, respectively. Drug content was near to 3 mg.mL⁻¹ for both formulations. Moreover, granules containing PHT-loaded nanocapsules increased the latency to myoclonic and generalized seizures in mice. Conclusions: The innovative use of nanocapsules to produce fluidized bed granules is an important technological approach to develop promising powders for reconstitution before oral administration, as pediatric and geriatric formulations.

Ethical approval: Ethics Committee of the University of Santa Maria (protocol #3273040416)
Financial support: CNPq/Brazil, FAPERGS and CAPES. E.G.O. Thanks CAPES/Brazil for the PhD scholarship.

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PRE-FORMULATION STUDY OF POLYMERIC FILM FORMING SYSTEMS FOR TOPIC ADMINISTRATION ROUTE

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Introduction: In the context of topical applications, polymeric film-forming systems are being exploited both in the treatment of dermatological diseases and the transdermal route of administration, as well as in cosmetic products as potential formulations to improve the inconveniences of topical application. Objectives: A pre-formulation study of properties of topically applied polymer systems. Methods: The developed system consists of solubilization of poly(vinil-alcohol) (PVA) in distilled water and polyvinilpirrolidone (PVP) in ethanol followed by the mixture of the 2 phases. The mixture was conducted by 2 different forms: under heating and under room temperature. The polymer proportion studied was 75% PVA / 25% PVP. Results and discussion: Through the results obtained by FTIR it is possible to observe that, regardless of the methodology of mixture, there is no difference in the composition. Thereby, methodologies, although different, do not cause chemical alteration, characterizing only a physical mixture of the polymer phases. By NMR it was possible to analyze the level of miscibility of these component phases. It was observed that the methodology of mixing under heating culminated in a greater miscibility of the systems, since, under temperature action, the PVA chains are more open, allowing the PVP chains to interpenetrate more easily, making the blends more homogeneous. In the results of XRD this hypothesis is confirmed, since higher degrees of crystallinity are found in the samples of mixture under heating, where a greater homogeneity resulted in a greater organization of the chains of the polymers, which was not seen in the samples mixed in under room temperature. Conclusions: The polymeric systems developed in this study highlights the importance of homogeneity of polymeric systems on the control of drug delivery, since higher homogeneity result in higher system crystallinity, an important parameter on the control of drug delivery. However, further studies are still needed in this pre-formulation phase to observe other relevant parameters.
A NOVEL AND MODERN PROPOLIS COMPRISING SYSTEM: RHEOLOGICAL ANALYSIS

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Introduction: Propolis (PRP) is a natural compound widely used due to its many biological activities. Its healing characteristic together with the anti-cancer and anti-inflammatory potentials highlight PRP to aid on the treatment of skin cancer. This drug is mainly utilized as ethanolic extract (PE), which has some disadvantages when topically applied. Hence, the development of film forming systems (FFS) to delivery PRP may allow to control the drug release, enhancing the availability and contact time. The use of polymeric blends may lead to advantageous rheological properties, thus the analysis of their behavior when mixed to PE presents great importance for the systems’ physical characteristics.

Methods: The FFS were prepared by two methods: cold one and solid dispersion, by the combination of poloxamer 407 (P407) and Carbopol 971P® (C971) or Carbopol 974P® (C974) or polycarbophil (PC). The PE, when added to the formulations, was 4, 8 or 12% (w/w). The rheological characterization was performed using a rheometer Haake-MARS II; cone-plate geometry (35 mm/2º angle), under the temperatures of 5, 25 and 32 ºC. It was evaluated the consistency index (k), flux index (n), hysteresis area (HA) and yield value (YV), for each formulations.

Results and discussion: Analyzing the continuous flow rheology it is inferable that all the formulations presented shear thinning behavior (n

Conclusion: The formulations containing PE presented ideal flow behavior for a topical application. Moreover, the cold method would be preferable to scaling up, once there were not any rheological differences between the formulations prepared by both methods.

COMPATIBILITY STUDY BETWEEN KAEMPFEROL AND EXCIPIENTS BY THERMAL, SPECTROSCOPIC AND CHEMOMETRIC METHODS

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Introduction: Kaempferol (KPF) has a wide range of pharmacological properties (e.g. anti-inflammatory, antibacterial, antiviral, antifungal, antiapoptotic and antioxidant) that turns out increasingly attractive the development of solid dosage forms containing this flavonoid. The development of new dosage forms is not a simple task, and involves many steps, including a preformulation study to obtain a suitable final product. In this regard, the compatibility study between drug and excipients is of great relevance. The present work aimed to evaluate, yet unexplored, incompatibilities between KPF and some of the most used excipients in solid dosage forms (starch, microcrystalline cellulose, magnesium stearate, hydroxypropylmethylcellulose, lactose, sodium lauryl sulfate and polyvinylpyrrolidone). Methods: Differential Scanning Calorimetry (DSC), thermogravimetry (TG), fourier transform infrared spectroscopy (FTIR) with support of two multivariate techniques: hierarchical cluster analysis (HCA) and principal component analysis (PCA), and quantitative assays by HPLC after isothermal stress testing (IST) were the tools employed. The studies were developed with binary mixtures of KPF:excipients in 1:1 (w/w) ratio. Results and discussion: according to DSC and TG results, KPF was found to present interactions with all excipient but microcrystalline cellulose. On the other hand, no incompatibilities with the excipients tested were observed when FTIR supported by multivariate data analysis was employed. The lack of incompatibility was confirmed by quantitative analysis after IST, that showed no significant changes in KPF content after HPLC assay. Conclusions: Although DSC/TG results suggested physical interaction of KPF with all but one of the excipients tested, this does not necessarily means a incompatibility. FTIR proved to be an important complementary technique to the DSC/TG, since the suspected incompatibilities were not fully confirmed. HCA/PCA techniques fulfilled their role as support tools in spectra interpretation, corroborating the importance of combining different techniques. Financial support: This work was supported by CNPq and CAPES/MEC.
SOLID LIPID NANOPARTICLES CONTAINING IRON OXIDE MAGNETIC NANOPARTICLES

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Introduction: The solid lipid nanoparticles (SLN) are a promising drug delivery system, as they combine advantages of other colloidal systems. Besides, they avoid problems of stability and scaling-up. Corroborating with the SLN properties, there are the magnetic nanoparticles (MNP) that shows low toxicity and enables magnetic targeting using an external magnet. In this sense, the association of MNP and SLN highlights the possibility of targeting the system to tissues difficult to reach; thus, allowing to release drugs exactly at the active site, reducing then the side effects. Methods: To prepare this system, the MNP were obtained by the coprecipitation method, in which two salts of iron are mixed in water, and then sedimented using NaOH (10 mol/L). The MNP dispersion was then used as the aqueous phase to prepare the SLN. The oily phase (tristearin) was heated up to 75 ºC, temperature that the watery phase (MNP + poloxamer 188 2,5%, w/w) was also taken and it was poured over the melted fat phase, this dispersion was homogenized at 15 rpm for 1 min and after sonicated (Miceron® Ultrasonic Cell Disruptor) at 7 kHz for 15 min. The MNP and SLN dispersions were also prepared separated for means of comparison. The mean diameter (MD) and the polydispersity index (PDI) of the systems were measured by photon correlation spectroscopy (PCS) (Zetasizer Nano S90) at 25 ºC. Results and discussion: The evaluation of the MD and the PDI of nanoparticles are important because these values provide the granulometric distribution and present the sample homogeneity. The PCS analysis allows the visualization of the SLN MD, which was 233,37 ± 10,50 nm and 0,300 for the PDI, while the MNP MD was 4,062 ± 0,143 nm and the PDI was 0,256. When the system prepared with both of the nanoparticles was prepared, the MD results for the SLN containing MNP were lower than the blank ones, presenting a value of 126,00 ± 5,72 and a PDI of 0,3. When the PDI is lower than 0,3, the preparation may be considered a monodisperse. Conclusion: The decrease on the MD suggest that the association of SLN with the MNP increase the organization of the system, and also that each MNP has the properties of a separate magnet performing attraction one another, thus reducing the average size of the SLN. The employed method was feasible as it was possible to obtain the SLN containing MNP. Although the results of MD decreasing are promising, further studies are necessary to understand this behavior of the systems.

MORPHOLOGICAL EVALUATION OF FILM FORMING CARRIERS WITH PROPOLIS EXTRACT

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Introduction: The topical chemotherapy shows promising results to the drug application against cancer directly on the skin, counteracting in an efficacious way the skin cancer. In this sense, the use of film-forming pharmaceutical carriers (FFS) presents many advantages, such as stabilizing drug molecules, which are protected by the film. They can also provide a controlled and/or sustained drug release, in a particular tissue, enhancing the availability and contact time of the formulation with the administration site. Propolis (PRP) is a compound with many biological activities, highlighting its anti-cancer and healing properties. The use of PRP as ethanolic extract (PE) in the bioadhesive/thermoreactive polymeric blends may corroborate with the structure of this system, guaranteeing a safe therapy on harmed tissues. Moreover, to the surface morphological analysis of the FFS, the scanning electronic microscopy (SEM) aids significantly on the observation of the surface homogeneity and failure absence. Methods: Binary polymeric blends of poloxamer 407 (P407) and Carbopol 971® (C971) or Carbopol 974P® (C974) or Polycarbophil (PC), with PE at the concentrations of 4, 8 and 12% (w/w) were prepared by the solid dispersion of P407/PE complex: F1 (P407:C971 and PE 4% w/w); F2 (P407:C971 and PE 8% w/w); F7 (P407:C974 and PE 12% w/w); F10 (P407:C974 and PE 12% w/w). The corresponding blank formulations were named B1/2; B7 e B10. Finally, the FFS were lyophilized for the microscopic evaluation of the morphology and surface by scanning electron microscopy (SEM). Results and discussion: The preparation method was efficacious, rendering formulations with homogeneity and with no precipitation of the PE. SEM results showed that all the formulations presented uniform surface. When observing the blank ones, it is noted that B10 shows a rougher surface than others. F1 and F2 displayed some porosity in the interface, which is visible on the inner region of the blank formulations, especially F1, with only 4% of PE. F7 and F10, show a laminar and organized interface. Conclusion: Thus, it is inferable that the formulations with higher concentrations of PE present an intern region more cohesive and interconnected, denoting less porosity. Therefore, considering PRP a resinous-wax compound, it can help on the system structure of FFS.
DEVELOPMENT OF SOLID DISPERSIONS OF URSOLIC ACID IN POLYVINYL PYRROLIDONE/POLOXAMER

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Introduction: Ursolic acid (UA) is a triterpenoid that exhibits various pharmacological effects, but it has low aqueous solubility which affects its therapeutic application. To overcome this problem, the purpose of this study was to develop solid dispersions (SDs) of UA using poloxamer 407 (PLX) and polyvinylpyrrolidone K30 (PVP).

Methods: The SDs were prepared by the solvent method. Drug and carriers were dissolved in dichloromethane which was removed by rotary evaporation. Physical mixtures (PMs) were prepared by mixture of pulverized drug and carriers. All formulations were prepared at the ratio UA:PVP:PLX (w/w/w) of 5:75:20(1) and 10:60:30(2). The aqueous solubility of UA in PMs and SDs was measured by adding the drug in excess to 2mL water on flask which was submitted to mixing with a shaker (50 rpm, 32.5°C, 48 h). The samples were filtrated, diluted and analyzed using HPLC. X-ray diffraction (XRD) was performed using Rigaku2000 (1.5406 Å, 40 kV, 30 mA) from 4° to 40° of 2θ and a step of 2°/min at 25°C.

Results and discussion: UA solubility (mg/mL) values in PM1 and SD1 were 2.12±0.01 and 3.51±0.02, and 1.75±0.08 and 3.05±0.01 for PM2 and SD2. The drug solubility increase was significantly (P < 0.05) greater in SDs than in PMs. XRD showed peaks attributable to UA in the PMs. On the other hand, absence of UA peaks in SDs indicated that crystalline drug was transformed to an amorphous dispersion after SD process.

Conclusions: Thus, the results obtained in this study showed that SDs is a promising strategy for to increase the solubility of UA.

Acknowledgments: This work was supported by FAPESP (São Paulo, Brazil), CNPq (Brasilia, Brazil) and CAPES (Brasilia, Brazil).

NANOCAPSULES WITH LACTONAS (NANOLAC) CURE TRYPANOSOMA CRUZI STRAIN RESISTANT TO BENZNIDAZOLE

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Introduction: Chagas disease remains neglected the only drug for its treatment in Brazil is the benznidazole, which causes side effects and low efficacy. We demonstrated that lactones (LAC) showed anti-T.cruzi efficacy in the acute phase (AP) and in the chronic phase (CP) in vivo. Nanocapsules (NC) were used as strategy for to load LAC due its lipophilic nature in order to control its release and reduce toxicity. The objective this study was to verify the effectiveness of free LAC and NCLAC by oral during the AP and CP in mice infected with VL-10 strain of T.cruzi treated for 20 days. Methods: Swiss female 20g were intraperitoneal inoculated with 10,000 trypomastigotes (AP) and 500 trypomastigotes (CP). The mice were divided: Free LAC 12, NCLAC (8 and 12), BZ100 mg/kg/day and controls. The treatment was assessed by hemoculture, PCR and ELISA. Results: Animals infected with NCLAC 12 showed 75% (AP) and 88% (CP) of cure. Animals treated with NCLAC 8 showed 38% of cure (AP) and 43% (CP); whereas mice treated with BZ were not cured. Free LAC none mice were cured. The qPCR technique had efficiency > 97.5%, these results strongly indicate absence of T.cruzi in the heart tissue in 100% of the treated animals infected with VL10 at both phases of infection, suggestive of parasitological cure. Conclusion: NC lead to increase of LAC therapeutic effectiveness in animals infected with T.cruzi strain totally resistant to BZ. These findings represent perspective for treatment of Chagas disease which still constitutes one serious neglected parasitic disease in the world.

Acknowledgements: the authors thank INCT-NANOFARMA (CAPES #2014/50928-2), FAPEMIG (APQ-02864-16), CNPq (310463/2015-7) and UFOP, Brazil, for financial support.
PHYSICOCHEMICAL CHARACTERIZATION, ANTIFUNGAL ACTIVITY AND CYTOTOXICITY OF SILVER NANO PARTICLES ESTABILIZED BY Caesalpinia ferrea (Tul.) Martius EXTRACT

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Background: Green synthesis is an ecological technique for the production of well characterized metallic nanoparticles using plants. This study aimed to investigate the synthesis of silver nanoparticles (AgNPs) using a Caesalpinia ferrea seed extract as a reducing agent. Methods: The formation of AgNPs was identified by instrumental analysis, including ultraviolet-visible (UV-Vis) spectroscopy, scanning electron microscopy (SEM), X-ray diffraction (XRD) of the AgNPs, and surface-enhanced Raman scattering (SERS) spectra of rhodamine-6G (R6G). The physicochemical characterization of AgNPs was studied, and its property as an antifungal agent against Candida albicans, Candida kruzei, Candida glabrata and Candida guilliermondii was evaluated. It was estimated the minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) values. Lastly, this study evaluated the cytotoxicity of the AgNPs in murine L929 fibroblasts cells using an MTT assay. Results and discussion: The UV-Vis spectroscopy, SERS, SEM and XRD results confirmed the rapid formation of spheroidal 30-50 nm AgNPs. The MIC and MFC values indicated the antifungal potential of AgNPs against most of the fungi studied and high cell viability in murine L929 fibroblasts. In addition, this study demonstrated that C. ferrea seed extracts may be used for the green synthesis of AgNPs at room temperature for the treatment of candidiasis. Conclusion: This study demonstrated that C. ferrea can be used for AgNP biosynthesis.

STUDY OF THE FORMATION OF INCLUSION COMPLEX BETWEEN CITRAL AND HYDROXYPROPYL-β- CYCLODEXTRIN

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Introduction: Citral (CTR) is a monoterpene has shown potential antimicrobial, anti-inflammatory and analgesic effects. However, CTR has high volatility and low solubility in water, which limits its use. In the context, this study was performed to elucidate the formation of inclusion complexes between CTR and hydroxypropyl-β-cyclodextrin (HP-β-CD). Methods: The inclusion complex was prepared by physical mixture (PM) and freeze-dried (FD) methods and characterized by fourier transform infrared absorption spectroscopy (FTIR) and scanning electron microscopy (SEM). The complexation efficiency was performed by high performance liquid chromatography (HPLC) through the preparation of a calibration curve. Results and discussion: The FTIR spectrum of FD showed interaction between CTR and HP-β-CD. Changes were observed in the morphology of particles in FD by SEM. From the calibration curve, a determination coefficient of 0.9992 was obtained and in the complexation efficiency values of 2.65% for PM and 71.66% for FD were obtained. Conclusions: The results of the analyzes suggest formation of inclusion complex between CTR and HP-β-CD by FD method. However, analysis by other techniques such as differential scanning calorimetry (DSC), X-ray diffraction (XRD) and nuclear magnetic resonance (¹H-NMR) its necessary to confirm the complexation.
NOVEL SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM OF BUTANOL FRACTION OF CALYCES FROM PHYSALIS PERUVIANA: FORMULATION, OPTIMIZATION AND MUCUS PERMEATION PROPERTIES EVALUATION

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Introduction: Butanolic fraction of calyces of *P. peruviana* has demonstrated promissory hypoglycemic activity in mice. Rutin, the major flavonoid of this fraction related to the hypoglycemic activity, has low aqueous solubility and stability which leads poor oral bioavailability. The aim of this work was to development and characterization of novel self-nanoemulsifying drug delivery systems (SNEDDS) containing a butanolic fraction of calyces from *P. peruviana* and evaluate the mucus permeation properties of this formulation. Methods: The composition of the SNEDDS was optimized using a three-factor, three level Box–Behnken design (BBD) and the optimized formulation was characterized for various parameters like droplet size, PDI, zeta potential and payload. Also it was performed mucus diffusion studies of the obtained formulation using transwell diffusion method. Results and discussion: It was obtained SNEDDS with droplet size ranged from 25 to 260 nm and negative zeta potential from -4 to -8. The amount of the oil, surfactant and Poly(dimethylsiloxane-co-(3-(2-(2-hydroxyethoxy)ethoxy)propyl)methylsiloxane) affect the droplet size, the highest effect was observed with the oil. The surfactant and co-surfactant influenced the zeta potential. The obtained SNEDDS loaded an appreciable percent of butanol fraction. According to the intestinal mucus diffusion study, the developed SNEDDS showed mucus permeation properties. The Poly(dimethylsiloxane-co-(3-(2-(2-hydroxyethoxy)ethoxy)propyl)methylsiloxane) had a high effect on this parameter. Conclusions: SNEDDS incorporating butanol fraction of calyces of *P. peruviana* have been successfully developed. This study demonstrated the potential of SNEDDS as an alternative for incorporating natural compounds with poor aqueous solubility. The Box–Behnken design was a very useful tool to optimize the SNEDDS formulation.

Acknowledgements: Dirección Nacional de Investigación Sede Bogotá Universidad Nacional de Colombia (DIB UNAL) for funding this research.

INCLUSION COMPLEX BETWEEN CITRAL AND β-CYCLODEXTRIN: CHARACTERIZATION AND IN VITRO CELL VIABILITY ASSAY

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Introduction: Citral (CIT) is a monoterpane formed by the geranial and neral stereoisomers, considered to be the major compound of the essential oil of *Cymbopogon citratus*, known as lemongrass, and has demonstrated potential antimicrobial, antitumor, anti-inflammatory, analgesic and antioxidant effects. However, CIT has low solubility in water and low bioavailability, which limits its use. Therefore, this study was performed to elucidate the formation of inclusion complexes between CIT and β-cyclodextrin (β-CD) to evaluate the cell viability. Methods: The physical mixture (PM) and freeze-dried (FD) of CIT/β-CD were obtained at molar ratio of 1:1, characterized by Fourier Transform Infrared spectrometry (FTIR), Scanning Electron Microscopy (SEM) and X-ray diffraction (XRD). The complexation efficiency were performed by High Performance Liquid Chromatography (HPLC). The cell viability (cytotoxicity) of free CIT and FD complex were evaluated in J774 macrophages cells. Results and discussion: The FTIR spectrum of FD showed interaction between CIT and β-CD. Changes in the particle morphology in FD were observed by SEM. Changes in β-CD crystallinity peaks were observed in FD by XRD analysis. From the calibration curve, a determination coefficient of 0.9992 was obtained, and in the complexation efficiency values of 1.32% for PM and 78.60% for FD were obtained. The cell viability assay did not demonstrate CIT and FD cytotoxicity. Conclusions: Analyzes demonstrated complexation of CIT with β-CD by FD and complex did not show cytotoxicity. Financial support: The authors are grateful to CAPES and CNPQ for financial support and fellowships.
PHARMACEUTICAL DEVELOPMENT OF CYCLODEXTRIN-BASED FURAZOLIDONE ORAL RECONSTITUTED SUSPENSION FOR TREATMENT OF CANINE CUTANEOUS LEISHMANIASIS

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Introduction: Canine cutaneous leishmaniasis (CCL) is a public health issue in Brazil and your occurrence in the State of Espírito Santo (ES) shows the clear relationship between infected dogs and the emergence of new human cases. Preliminary studies showed the successful use of furazolidone (FZD) as antileishmanial agent for the treatment of CCL. The aim of this study was to develop oral suspensions based on FZD-β-cyclodextrin complexes (60 mg/mL) for the further efficacy study in dogs naturally infected with CCL. Methods: The inclusion complex FZD:βCD was prepared by utilizing of kneading method with weight ratio of 1:2. The suspension was developed using sodium CMC as suspending agent (0.5% w/V) and Tween 80® as wetting agent. The suspension was flavored with flavor of meat, specific for veterinary use. The physical stability of reconstituted suspension was characterized regarding pH, viscosity, particle size, zeta potential and sedimentation volume (24 h). Results and discussion: The pH values for pure vehicle and for reconstituted suspension were 5.66 and 5.94, respectively. The particle size was 16.20 µm (SD± 14.32 µm) and zeta potential was -59 mV (SD± 3,91 mV). Percent sedimentation volume after 24 h was 24%. Vehicle viscosity at 30 rpm was 1643 cP (spindle L34). The suspension vehicle showed pseudoplastic behaviour. Conclusions: The values found for the parameters studied are in agreement with data from the literature and suggest that the suspension presented physical stability suitable for the intended use. A method for quantification of the drug in the reconstituted suspension is being developed and validated.

Acknowledgments: This research was supported by FAPES and FAP/PRPPG-UFES.

PHYSICAL STABILITY OF ORAL RECONSTITUTED SUSPENSION CONTAINING ALBENDAZOLE FOR USE IN COMPANION ANIMALS

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Introduction: A challenge for pharmacists is to provide pharmaceutical dosage forms suitable for patients with different therapeutic needs including animals. Companion animals are playful which makes their handling difficult, especially for the administration of drugs. The aim of the present work was to evaluate the physical stability of reconstituted suspensions for oral use containing albendazole for the treatment of endoparasites in Pets. A flavor agent for animal use was employed. Methods: The suspensions were developed using sodium CMC at concentrations of 0.3, 0.4, 0.5 and 0.6% w/v as suspending agent, and the formulations were named SUSP1, SUSP2, SUSP3 and SUSP4. The physical stability of reconstituted suspensions were characterized regarding appearance, pH, viscosity, sedimentation volume (2, 4, 6, 8 and 48 h) and reconstitution after 48 h. Results and discussion: Oral viscosity plays an important role in the perception of the texture in liquid dosage forms. According the results, all formulations presented pseudoplastic behaviour and the viscosity was higher in SUSP4 due to the higher concentration of sodium CMC. Percent sedimentation volume of suspensions after 8 h were 76, 98, 96 and 98% for SUSP1, SUSP2, SUSP3 and SUSP4, respectively. After 48 h, the percent sedimentation volume were 16, 24, 28 and 36%. The redispersibility results indicated the formulations SUSP3 and SUSP4 showed short redispersion times (11 and 15 s). Formulations 1 and 2, however, required vigorous agitation (27 s) to resuspension, supposedly due to more compacted sediment. The incorporation of albendazole did not change the pH value of the vehicle and remained around 5.6 to 5.8. Conclusions: Analysis of the results to sedimentation and reconstitution tests suggests the occurrence of a compact sediment to SUSP1 and SUSP2, that presented cloudy supernatant. For SUSP4 a voluminous sediment was observed and a cloudy supernatant. Only SUSP3 presented voluminous sediment and clear supernatant.

Acknowledgments: This research was supported by FAPES and FAP/PRPPG-UFES.
SWELLABLE FILMS FOR INCORPORATION OF NANOPARTICLES AND APPLICATION IN THE TREATMENT OF WOUNDS

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Introduction: Impaired wound healing represents a biomedical burden, and the need for dressings with improved performance, swellability and flexibility stimulates continuous research. In this study, hybrid films containing nanoparticles were developed to promote absorption of the excess of wound exudate while releasing a synergistic combination of drugs for promotion of healing.

Methods: The films were obtained using sodium alginate, CaCl₂, monoolein, glycerol and/or propylene glycol. A combination of antioxidants (vitamin E and quercetin) that act synergistically and an antimicrobial essential oil were incorporated directly to the films or encapsulated in nanostructured lipid carriers composed of shea butther and argan oil, which were subsequently included in the films. The influence of composition on the swelling and in vitro drug release was evaluated for up to 48 h.

Results: Increasing glycerol concentration in the film from 5 to 20% increased water absorption by 2-fold; a less pronounced increase (1.4-fold) was observed when glycerol was replaced by propylene glycol, while incorporation of monolein reduced the maximum amount of water absorbed by 1.6-fold. The swelling followed a second order kinetics, with the formation of plateau after 24h. The films containing glycerol were able to sustain the antioxidants release, with 40% of the drugs released within 48 h. A slower release was observed upon drug encapsulation in the nanocarriers. Conclusions: The results demonstrated the importance of a careful design to maximize swelling properties of films, and the feasibility of nanoparticle incorporation in the films to slow down drug release. This study was considered exempt from IACUC, and funded by FAPESP (2013/16617-7); J. Mattos and S. Fernandez received fellowships from FAPESP (2017/19059-6) and CAPES.

TOXICITY EVALUATION OF DITERPENE-LOADED NANOSTRUCTURED LIPID CARRIER IN ZEBRAFISH MODEL

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Introduction: Phytol is a diterpene which has numerous pharmacological activities, such as anti-inflammatory and analgesic. The literature reported Nanostructured Lipid Carriers (NLC) as drug delivery systems improving the stability and pharmacological activity of diterpenes. Therefore, it is necessary to verify the safety of this system. Due to this, zebrafish emerge as in vivo model for screening of toxicity of nanocarriers Thus, this work aimed to evaluate the toxicity of phytol-loaded NLC in zebrafish model.

Methods: The empty-NLC and phytol-NLC were prepared by the hot homogenization method at 65°C. The zebrafish assays were approved (number 1369/15) by the local animal welfare ethical committee (DEC) of Butantan Institute and were realized according to Guidelines for the Testing of Chemicals (OECD), number 236. The assays were conducted in 24-well plates with five embryos per treatment/concentration at 28°C. Before being diluted in E2 medium (control), phytol oil was diluted in 0.25% DMSO. Embryos were exposed at 0.095, 0.475 and 0.95µg/mL in quadruplicate. After treatment, each embryos and larvae were monitored with a fluorescence microscope for 24, 48, 72, 96 h post-fertilization, for evaluation of mortality and malformations.

Results and discussion: The zebrafish embryos were exposure to empty-NLC, phytol oil and phytol-NLC. There was not significant difference in survival at all concentrations when compared to control group and no malformation was observed. Conclusion: This work highlights phytol-loaded NLC are not toxic at all concentrations tested and can be a promisor drug delivery system and safe.

Financial support and acknowledgements: CAPES, CNPq, FINEP, FAPITEC/SE, REDE ZEBRAFISH OF THE IMMUNO-REGULATION UNIT, SPECIAL LABORATORY OF APPLIED TOXINOLOGY (CEPID/FAPESP), BUTANTAN INSTITUTE OF SÃO PAULO
FORMULATION DESIGN AND CHARACTERIZATION OF NANOSTRUCTURED LIPID CARRIERS CONTAINING RETINOIC ACID FOR ACNE TREATMENT

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Retinoic acid (RA) is a broadly used drug for acne treatment. However, treatment with RA causes serious side-effects. Therefore, the objective is to develop and characterize a formulation of nanostructured lipid carriers containing RA (NLC-RA) that may promote less skin irritation. A 2³ factorial design was performed, where the influence of surfactant (Tween 60 and Brij 58), liquid lipid concentration (0.4% and 1.2%) and RA concentration (0.05% and 0.1%) was evaluated. The response was the RA encapsulation efficiency (EE%) after 30 days. The formulations were prepared by hot homogenization method and characterized by diameter, polydispersity index (PI), zeta potential (ZP) and transmission electron microscopy (TEM). A degradation study with 2,2’-Azobis (2-methylpropionamide) dihydrochloride (AAPH) was carried out to compare the NLC-RA with a solid lipid nanoparticles formulation containing AR (SLN-AR). The factors studied had a statistically significant influence on the response, with the surfactant being more important (26%), followed by the liquid lipid concentration (-8%) and the RA concentration (6%). The formulation with the best response (EE% = 97 ± 1%) presented a diameter = 143 ± 8nm, PI = 0.5 ± 0.1 and ZP = +31 ± 1mV.

The TEM images show NLC-AR vesicles in spherical shape and homogeneous distribution. It has been found that NLC-RA formulation exerts greater drug protection when compared to an SLN-AR formulation. After 30 days, no significant changes of the diameter, PI and ZP were observed, which demonstrates system physicochemical stability. As perspective, in vitro and in vivo evaluation of formulation skin irritation is required.

Financial support and acknowledgements: Capes, CNPq and Fapemig

STIMULI-RESPONSIVE AND MUCOADHESIVE LYOTROPIC LIQUID CRYSTALS FOR THE TREATMENT OF VAGINAL INFECTIONS

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Introduction: Topical vaginal treatment increases the amount of available drug in the vaginal cavity and reduces systemic side effects related to oral administration. However, vaginal fluids generally dilute conventional dosage forms, yielding leakage, messiness, and erratic doses. Therefore, mucoadhesive systems have been developed as a strategy to prolong the retention time of drug delivery systems. In addition, this work aimed to develop a stimuli-responsive system that could be generated in contact with temperature and the aqueous media of the vaginal environment.

Methods: Formulations were produced by combining oleic acid and cholesterol (7:1) as oil phase, a poloxamer solution at 16% (w/v) as aqueous phase and ppg-5-ceteth-20 as surfactant. An isotropic system was chosen from the phase diagram and in order to mimic the vaginal environmental conditions, a simulated vaginal fluid (SVF) was added to the formulation. Small-angle x-ray scattering (SAXS), Polarized light microscopy (PLM), continuous and oscillatory rheology measurements, texture profile and mucoadhesive assay were performed in order to characterize the obtained systems.

Results and discussion: SAXS and PLM studies indicated the isotropic system was stable, easily administrable and exhibited promissor mucoadhesive properties.
pH SENSITIVE MICROPARTICLES AS DELIVERY SYSTEM OF AN HYPOGLYCEMIC FRACTION OF CALYCES FROM Physalis peruviana

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Introduction: Physalis peruviana L. (Cape gooseberry) is a plant widely cultivated in the Andean mountain in South America and its calyces are the main by-product of the harvest and commercialization of the fruits. Previous studies had demonstrated that the butanolic fraction of the calyces exhibit hypoglycemic activity, the flavonoid rutin has been related to this activity. Since rutin is extremely acid-labile, the aim of this work was to develop and to optimize a pH sensitive microparticulated system containing the butanolic fraction of calyces. Methods: Hypromellose phthalate (HPMCP) microparticles loaded with butanolic fraction were elaborated by emulsification-evaporation method. Plackett-Burman and Box-Behnken statistical experimental designs, were employed to development and optimization of HPMCP-microparticles. Microparticles were characterized their size, morphology, entrapment efficiency, drug loading, release profile and yield. Results and discussion: According to Plackett and Burmann experimental design concentration of HPMCP (%), concentration of PVA (%) and organic phase (%) were the factors with the greatest effect on entrapment efficacy of BPFF. HPMCP-microparticles loaded with butanolic fraction shown size between 1 and 7 µm, entrapment efficiency ranged from 30 to 75% and yield between 20 and 76%. In addition, the optimized microparticles exhibit a release of less that 8% of the rutin at acidic pH. Conclusions: Development and optimization of microparticulate with rutin from P. peruviana is an important contribution to improve the stability of rutin at gastric pH and therefor its bioavailability. Acknowledgements: Dirección Nacional de Investigación Sede Bogotá Universidad Nacional de Colombia (DIB UNAL) for funding this research.

PREPARATION, CHARACTERIZATION AND CELL VIABILITY EVALUATION OF MORIN / HYDROXYPROPYL-β-CYCLODEXTRIN INCLUSION COMPLEX FOR DISSOLUTION AND BIOAVAILABILITY ENHANCEMENT

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Introduction: Morin is a flavonoid that shows several pharmacological activities such as antioxidant, anti-inflammatory, anticancer and antibacterial. However, morin has low solubility in water. Thus, the complexation of morin in hydroxypropyl-β-cyclodextrin (HP-β-CD) can improve its solubility, oral bioavailability and consequently, the pharmacological effects. Methods: The inclusion complex (IC) was prepared by freeze-drying method and was characterized by differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction (PXRD), scanning electron microscopy (SEM) and nuclear magnetic resonance (NMR). The analytical method to morin quantification was developed and validated by high performance liquid chromatography (HPLC), which used to determine the complexation efficiency and the in vitro dissolution profile. Cell viability was evaluated by the resazurin reduction assay in J774 macrophages cell line and the irritation potential was evaluated by the HET-CAM technique. This project was submitted to conduct the pharmacokinetic (oral bioavailability) studies to the ethical committee. Results and discussion: The physical-chemical and morphological characterization results suggested that the morin was entrapped into HP-β-CD cavity, indicating the formation of IC. The complexation efficiency was 98.3%. The IC exhibited a faster dissolution, achieving the maximum dissolution of 97.84% at 240 minutes. The IC showed high capacity to maintain cell viability, obtaining resazurin reduction of 98 – 99% at all concentration evaluated. HET-CAM tests demonstrated that the IC is a formulation without irritation potential (irritation score = 0). Conclusions: The IC is a promising formulation which able to increase the morin bioavailability and pharmacological effects, further, it will be confirmed by pharmacokinetic studies.
INVESTIGATION OF HESPERETIN INCLUSION COMPLEXES WITH γ-CYCLODEXTRIN AND HYDROXYPROPYL-γ-CYCLODEXTRIN: DEVELOPMENT AND CHARACTERIZATION

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Introduction: Hesperetin (HT) is a flavonoid found abundantly in citrus fruits and it has pharmacological effects, such as antioxidant, anti-inflammatory, antiplatelet and vasoprotective. This compound has low solubility in water. In this way, the complexation of HT with cyclodextrins can improve its physical-chemical characteristics.

Methods: The complexes were obtained with γ-cyclodextrin (γ-CD) and hydroxypropyl-γ-cyclodextrin (HP-γ-CD) by freeze-drying method. Then, the samples was characterized using differential scanning calorimetry (DSC), thermogravimetry/derivative thermogravimetry (TG/DTG), fourier-transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM). The complexation efficiency was evaluated by high performance liquid chromatography (HPLC) with an analytical method developed and validated previously.

Results and discussion: The HT DSC curves displayed endothermic peak at 246 °C corresponding to the melting point. However, in the DSC curve of HT/γ-CD and HT/HP-γ-CD inclusion complexes, the endothermic peak of HT completely disappeared. FTIR spectra showed that some bands of HT were absent in both complexes samples. HT/γ-CD and HT/HP-γ-CD TG/DTG curves showed decrease of weight loss because in the complexation process some of water molecules are replaced by hydrophobic molecules. SEM micrographs of HT/γ-CD and HT/HP-γ-CD complexes showed that the original morphology of both molecules disappeared, forming a new structure organized in blocky. The complexation efficiency were 72 and 98% for HT/γ-CD and HT/HP-γ-CD, respectively.

Conclusions: The results suggest that there was the formation of inclusion complex with HT/γ-CD and HT/HP-γ-CD by freeze-drying method.

EV ALUATION OF IN VITRO RELEASE AND PERMEATION OF CORDIA VERBENACEA DC ESSENTIAL OIL FROM TOPICAL SEMISOLID DOSAGE FORMS

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Cordia verbenacea DC. (CV) essential oil is indicated for the treatment of inflammatory conditions. The anti-inflammatory effect has been mainly associated with the presence of sesquiterpenes humulene (HUM) and caryophyllene (CAR). In 2005, was launched on the market the first fully developed herbal medicine in Brazil, the Acheflan® cream and aerosol containing 0.5% CV, of dermal application for the treatment of muscular pains and bruises. In this work, was developed formulations such nanoemulsions containing 0.5% CV. In addition, it was compared with the commercial dosage forms in relation to in vitro performance (release and permeation) using vertical Franz-type diffusion cell. The quantification of HUM and CAR was performed through HPLC-DAD. In the permeation and release assays, the chosen receptor medium was 0.1 M phosphate buffer with 2% PEG-40 and 20% ethanol for presenting sink conditions. The membranes used in the in vitro permeation and release assays were porcine epidermis and silicone membrane, respectively. The cream and aerosol exhibited low release and permeation. So, was evaluated the in vitro performance of the essential oil of CV which presented good intrinsic capacity of penetration through the membranes. From this, new formulations such as nanoemulsions, with different compositions and 0.5% CV were developed to overcome the permeation and release difficulties presented by commercial formulations. Two nanoemulsions presented adequate droplet size, polydispersity index and pH. These two formulations showed higher and statistically different in vitro release permeation values of the commercial formulations. This indicates that the compositions of the formulations may influence the delivery of the oil components from the vehicle to membranes.
LECITHIN-BASED MICROEMULSION STABILITY AGAINST GASTRIC AND INTESTINAL FLUIDS

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Microemulsions (ME) are colloidal dispersions used to enhance drug solubility and permeation. Lecithin is a biocompatible product with the ability to block P-gp receptors, which are efflux transporters that reduce drug bioavailability. Thus, the aim of this work was to evaluate the stability of a lecithin-based ME against simulated gastric and intestinal fluids. ME batches were prepared through sonication followed by ultrasound bath. Afterwards, the simulated gastric (SGF) and intestinal (SIF) fluids were prepared accordingly to the US Pharmacopeia with few modifications. Majorly, no enzymes were added, and SGF with final pHs of 1.2 and 4 were prepared. Initially, the blank ME were fully characterized. However, for the stability study only droplet size was evaluated (NanoZS, Malvern® - All analyses were made at 1:40 v/v dilution). The prepared ME were translucid with a Z-average of 21.2 ± 0.2 nm, a polydispersity index (PdI) of 0.117 ± 0.034 and a zeta potential of -2.46 ± 2.51 mV. At the end of the experiment, no significant changes in the values of the droplet size were observed (ANOVA+Post-hoc Tukey; p>0.05). Indeed, the Z-averages after two hours in SGF at both pHs (1.2 and 4) and after six hours in SIF were 23.3 ± 0.3 nm, 21.9 ± 0.3 nm and 21.9 ± 2.0 nm, respectively. Similarly, the PdI remained unchanged, 0.184 ± 0.031, 0.168 ± 0.028 and 0.076 ± 0.012 nm for SGF at both pHs and for SIF experiments, respectively. As a perspective of this work, drugs will be loaded at the ME in order to evaluate their release and stability.

DEVELOPMENT OF AN IN-SITU GELLING LIQUID CRYSTALLINE SYSTEM FOR NASAL DELIVERY OF DONEPEZIL

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Donepezil is a drug usually administered in the Alzheimer’s disease treatment that acts as an acetylcholinesterase inhibitor in the brain, enhancing the cholinergic activity and relieving the symptoms related to disease. Donepezil has been administered by immediate release solid oral dosages but several gastric side effects have been reported. In order to overcome such limitations, new release systems and alternative routes of administration have been explored. The nasal route presents many advantages such as overcoming gastric and blood-brain barrier problems, through a direct connection between the brain and the nose, which facilitates the transport of drugs to the central nervous system, but limits the drug availability due to mucociliary clearance. The aim of this study was to develop a in situ gelling liquid crystalline system for nasal delivery of donepezil. For this, a pseudoternary phase diagram was constructed mixing different combinations of polyethylene glycol hexadecyl ether (CETETH- 10), oleic acid and water. The systems were characterized by polarized light microscopy and lyotropic liquid crystalline (LLC) precursors were selected. These LLC precursors were submitted to gelling test with artificial mucus and the system containing 45% of oleic acid, 50% of Ceteth10 and 5% of water was gelated with the lowest proportion of mucus (1:10). Drug loading study was performed and the samples containing up to 9 mg/g of donepezil were clear and fluid. The gelled systems were analyzed for the texture and mucoadhesion profile using porcine mucosa, demonstrating mucoadhesive properties. The results demonstrated that the selected LLC precursor has potential for intranasal administration of donepezil. Rheological analysis and in vitro release studies will also be performed.

Financial support: Capes
PLGA NANOPARTICLES LOADED WITH NEW THIOUREA DERIVATIVE: DEVELOPMENT, CHARACTERIZATION AND IN VITRO EVALUATION AGAINST Leishmania amazonensis

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Introduction: Leishmaniasis is a neglected disease caused by protozoan parasites belonging to the genus Leishmania. Currently, the drugs available for its treatment present high toxicity, along with development of parasite resistance. Recently, our group synthesized a series of N,N'-disubstituted thioureas which were evaluated in vitro against Leishmania amazonensis. The N-(3,4-Methylenedioxyphenyl)-N'-(2-phenethyl)thiourea displayed an excellent antileishmanial activity. Drug delivery systems, as nanoparticles (NPs), present an opportunity to potentiate the therapeutic effect of antileishmanial compounds. This work describes the development of PLGA NPs loaded with thiourea. Methods: NPs were prepared using the nanoprecipitation combined with solvent evaporation technique. They were characterized for size, charge, transmission electron microscopy (TEM), yield (% w/w) and drug entrapment efficiency. The in vitro activity (Protocol number: 030/17) of blank and thiourea-loaded NPs on L. amazonensis was determined in the promastigotes and amastigotes model and the cytotoxicity activity on bone-marrow derived macrophages of mice BALB/c. Results: The developed thiourea-NPs were monodispersed with mean diameter < 200 nm and exhibited negative zeta potential (-30 mV). They have relatively higher yields (87% w/w) and drug loadings ranging from 30% w/w. TEM revealed that NPs had smooth surface and spherical topography. In the in vitro test was observed that thiourea-NPs show a potential antileishmanial activity against intracellular L. amazonensis (IC₅₀ = 1.2 μg/mL ± 0.2) and no cytotoxicity (CC₅₀ > 100 μg/mL). Conclusion: Therefore, these results demonstrated that the nanoprecipitation method was efficient to produce thiourea-loaded NPs with a promising antileishmanial activity.

DEVELOPMENT AND IN VIVO EVALUATION OF ORAL NANOCOMPOSITES OF BABASSU AND COPAIBA OILS ASSOCIATION FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

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Benign prostatic hyperplasia (BPH) is a common condition in men from the sixth life decade, characterized by benign prostate growth¹. Traditional pharmacotherapy includes 5α-reductase inhibitors and α-adrenergic blockers, which have demonstrated several collateral effects². Studies point to babassu oil (BBS) association with copaiba oil-resin (COPA) as a potential phytotherapeutic association for treatment and prophylaxis of BPH³, although few studies have been published with nanosystems containing this association. In this work, we propose the development and evaluation of polymeric nanocomposites of lamellar silicates containing BBS and COPA oils, in order to enhance their anti-hyperplastic activity. Three groups of organoclay-based nanocomposites (Viscogel B8®, S4®, S7®) were prepared by the intercalation method⁴ in polyethyleneimine solution of low or high molar mass polymer (PEI-BMM or AMM, respectively), acetone and the oils of BBS or BBS-COPA. Intercalation efficiency and X-ray diffraction characterized the nanocomposites. The best experimental conditions were analyzed by Fourier transform infrared (FTIR), differential scanning calorimetry (DSC) and in vivo tests (Protocol number: 035/14). The adopted method for intercalated nanocomposites formation was appropriate. Nanocomposite containing oils association (BBS-COPA) with VS7 clay and PEI-BMM, presented the highest intercalation efficiency values of BBS (83.08% ± 0.10) and COPA (70.14% ± 0.88) and showed the highest interlamellar spacing (41.67 Å). The FTIR and DSC techniques confirmed the oils intercalation in organoclay. Also, the nanocomposite has demonstrated prostatic volume reduction in 16.13%, similar result as obtained with finasteride (17.13%). These results suggest that the developed nanosystem presents therapeutic potential in BPH, although complementary studies are required.

Acknowledgements: CNPq, CAPES, FAPERJ and UFRJ.

ANTIMICROBIAL ACTIVITY OF TEA TREE OIL NANOPARTICLES IN SEPSIS

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Introduction: The tea tree oil (TTO), which is extracted from Melaleuca alternifolia, has shown potential anti-inflammatory, antibacterial, antifungal, and analgesic activities. On the other hand, essential oils typically exhibit low solubility and high volatility, limiting its use as a therapeutic agent. Colloidal drug delivery carrier present advantages such as drug release control, improved efficacy and physicochemical stability. Nanoemulsions (NE) are composed of vegetal, synthetic, or semisynthetic oils stabilized by surfactants. Nanocapsules (NC) consist of an oily or aqueous core surrounded by a polymeric wall. The aim of the present study was to develop and characterize NE and NC formulations containing TTO and evaluate the antibacterial activity in sepsis model.

Methods: TTO-NE e TTO-NC were prepared by spontaneous emulsification and nanoprecipitation method, respectively. The effect of solvent (ethanol or propylene glycol), surfactant type and concentration (Tween 80®, Pluronic F68®, 0.5%, 1% or 1.5%) and polymer type in NC (Eudragit RS100®, polycaprolactone) on the physicochemical properties (particle size, polydispersity index, PDI, and zeta potential) of nanocarriers was evaluated. The effect of TTO-NE, TTO-NC and TTO free in septic rats was evaluated by puncture model.

Results and discussion: Pluronic F68® 1.5% and ethanol provided lower particle size (170-200 nm) and polydispersity index (0.1-0.2). Eudragit-based nanocapsules showed more reproducible physicochemical properties than PCL-based nanoparticles. The NE-TTO and NC-TTO reduced the bacterial growth when compared with the control group.

Conclusions: NE-TTO and NC-TTO showed to be promising carriers for TTO delivery.

Ethical approval: CEUA UFSC PP00953

NANOEMULSION LOADED WITH BIOACTIVE NITROAROMATIC COMPOUND: FORMULATION DEVELOPMENT AND BIODISTRIBUTION STUDY

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Introduction: Nitroaromatic derivative 4-(chloromethyl)-3-nitro-N-(2-hydroxiethyl) benzamide (CNB) showed a promissor antitumor activity in solid tumors and reduced systemic toxicity. However, CNB is poorly soluble in aqueous medium which represents a major challenge for intravenous administration. In this study, we developed a nanoemulsion loaded with CNB (NE-CNB) in order to allow its administration by intravenous route.

Methods: NE-CNB formulations were prepared by the the hot melt homogenization method following by ultra-sonication and characterized by diameter, polydispersity index (PI) and zeta potential. The CNB concentration was determined by high performance liquid chromatography. After radiolabeling of NE-CNB with technetium-99m, circulation time was determined by measuring blood activity from healthy animals. In addition, biodistribution studies and scintigraphic images were carried out in tumor-bearing Swiss mice at 0.5 and 1h after injection of NE-CNB.

Results and discussion: Diameter, IP and zeta potential of 135 ± 9 nm, 0.19 ± 0.03 and -20 ± 8 mV, respectively. The concentration of CNB-loaded NE was about 2.5 mg/mL. No significant variation in globule mean diameter, PI, and zeta potential values over 28 days was observed. Blood levels of NE-CNB decrease in a biphasic manner with an α and β half-life of 2.3 and 43.3 min. Biodistribution data and scintigraphic images showed pronounced uptake in the liver, kidneys and intestine. In addition, tumor uptake was greater than control tissue, resulting in high tumor-muscle ratio, which indicates greater specificity for the tumor area.

Conclusions: NE formulation can be a good strategy to the association of CNB, and to allow its intravenous administration. Ethical Committee of Animal Welfare UFMG approval protocol nº 323/2016.

Acknowledgments: FAPEMIG, CAPES.
OBTEINING, CHARACTERIZATION AND EVALUATION TOXICITY OF (-)-LINALOOL-LOADED NANOCAPSULES IN THE ZEBRAFISH MODEL

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Introduction: (-)-Linalool is an acyclic monoterpene have antinociceptive, antihyperalgesic, antidepressivas and anti-inflammatory activities. However, high volatilization and low solubility in water of this compound limit its use. An alternative to overcome the physico-chemical limitations of this compound is encapsulation in polymeric nanocapsules. Thus, the objective of this study was to develop and characterize (-)-linalool-loaded nanocapsules and investigate its toxicity using zebrafish embryos. Methods: The nanocapsules were prepared by method interfacial deposition of preformed polymer. The zebrafish assays were approved by the local animal welfare ethical committee of Butantan Institute (number 1369/15) and were realized according to OECD guideline. Assays were conducted in 24-well plates with five embryos per treatment/concentration at 28°C. Before being diluted in E2 medium (control), (-)-linalool was diluted in 0.25% DMSO. Embryos were exposed at 0.188, 0.375 and 0.95µg/mL in quadruplicate. After treatment, embryos and larvae were monitored with a fluorescence microscope for 24, 48, 72, 96 hours post-fertilization, for evaluation of mortality and malformations. Results and discussion: The nanocapsules had a particle size of 199.1 nm and PDI of 0.13 nm. In the in vitro release study, nanocapsules showed sustained release profile of the (-)-linalool after 24 hours, different from that observed free (-)-linalool, which showed a fast release in 6 hours. Regarding the toxicity assay, no malformation was observed in zebrafish embryos when exposure to linalool oil, and linalool nanocapsules. Conclusion: The nanocapsules containing (-)-linalool may promising and safe therapeutic alternative source and further studied in clinical trials also need to explore this (-)-linalool compound.

NANOCOMPLEXES BASED ON CHITOSAN: MUCOADHESIVENESS AND STRUCTURAL PROPERTIES

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Introduction: Nanostructured polyelectrolytes complexes (nano PECs) are built through supramolecular interactions, by mixture oppositely charged polyelectrolytes. Nano PECs structural arrangement impact their physicalchemical (PQ) and functional properties. The knowledge of the structure and its correlation with the PQ properties is crucial for the design of drug delivery systems with modulated properties to specific biological applications. Computational study is a promising tool to predict structural properties of such systems. Chitosan(CS), hyaluronic acid(HA) and hypromellose phthalate(HP) were exploited to compose nano PECs with methotrexate (MTX). Methods: Nano PECs were obtained by polyelectrolyte complexation and characterized by diameter (D)/zeta potential (ZP) on Zetasizer nano ZS. Mucoadhesive and structural properties of complexes was evaluated by mucin adsorption assay in pH 1.2 and 6.8. Structural properties of nano PECs was estimated by computational studies, performed at the semi-empirical level using MOPAC computational package. Results: Nano PECs D and ZP ranged from 256.07 to 323.67 nm and +19.95 to +25.55 mV, respectively. A greater interaction with mucin occurred at pH 6.8. From computational studies, the most favourable organization of the CS/HA/HP/MTX complex was predict as linear HA structure inside the cavity of helix structure of CS. The other hand, HP and MTX were outside the CS cavity. Conclusion: Nano structures based on CS were successfully prepared by polyelectrolyte complexation. Mucoadhesiveness of complexes was demonstrated. Computational studies were a valuable tool to predict the structural properties of nano-PECs. Acknowledgements: FAPESP; INCT.
DEVELOPMENT OF ETHYLCELLULOSE MICROPARTICLES CONTAINING PRAZIQUANTEL

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Introduction: The preparation of microparticles containing praziquantel (PZQ) by emulsion solvent evaporation technique is an alternative to improve the drug stability and mask the bitter taste, aiming the development of new oral dosage forms. Methods: The microparticles were prepared by a factorial design of 2^4 + 2C defined in levels of -1, 0 and +1 wherein the ratios of the independent factors composed for ethylcellulose (EC) EC: PZQ and Tween 80® were 1.5%, 1.0% and 1.5% (w/w). The preparation of eight formulations, controls (F1, F2, F3, F4, F6, F7, F8 and F9) and two central-point formulations (F5 and F10) were accomplished using two stirring techniques (mechanical and magnetic) at 800 rpm. Then, they were submitted to vacuum filtration, dried in desiccator, and stored with light protection. Results: The formulations prepared using magnetic stirring displayed better yield for F8 (98.4%), justified for the ratios of Tween 80® and PZQ at 1.50% and 1.25% (w/w). Mechanic stirring preparations presented good yield for F9 (80.6%) at the ratios of Tween 80® and PZQ (1.50: 1.50% m/m). Scanning electron microscopy analysis showed microparticles obtained by magnetic stirring exhibiting predominantly spherical shape and sizes of 5-10 μm arranged in agglomerates. Moreover, it shows high PZQ adsorbed on surface. On the other hand, microparticles obtained by mechanical agitation presented a regular spherical surface with size of 3 μm to the majority of the particles, which presented high porosity showing PZQ trapped on the surface and in the hollow spaces. Thus, the reduction of particles dimensions can be observed when the mechanical stirring method was used. Conclusion: The experiment showed that it was possible to obtain EC microparticles containing PZQ using both techniques of stirring, but dependent of the ratios of substances Tween 80® and PZQ. The high porosity observed could be an indicative that taste masking can be achieved. The ideal proportion of PZQ and Tween 80® was found to be 1.50% (w/w), providing yields higher than proportions of 1.25 % and 1.0 %. The mechanical stirring was more suitable compared to the magnetic to obtain microparticles with size and regular surface area although magnetic stirring process showed higher yield.

PREPARATION AND CHARACTERIZATION OF DOXORUBICIN-LOADED PH-SENSITIVE MICELLES FOR APPLICATION AS A THERANOSTIC PROBE

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Introduction: Doxorubicin (DOX) is an antibiotic, from anthracycline family, widely used in breast cancer chemotherapy. However, due to nonspecific distribution, it exhibits serious adverse effects such as hepatotoxicity, myelosuppression, and cardiotoxicity. The development of polymeric micelles (PMs) is a strategy used for the delivery of DOX to tumors, thereby improving its efficacy and reducing side effects. Adding a specific stimuli-triggered drug release mechanism, like pH-sensitivity, is an interesting approach for targeted therapy. pH-sensitive micelles remain stable at physiological pH and destabilize at acidic pH, releasing the encapsulated drug. Furthermore, the functionalization with the radioisotope 99mTc allows monitoring the fate of PMs in the body and early feedback on treatment efficacy. Thus, the aim of this study was to develop and characterize pH-sensitive micelles loading DOX for further application as a theranostic probe. Methods: PMs were prepared using a solvent evaporation method. Micelles content include 5% of DSPE-DTPA to allow further radiolabeling with technetium-99m. Micelles were characterized by particle size and zeta potential. The critical micelle concentration (CMC) was determined by spectrofluorimetry, using pyrene as a fluorescent probe. The encapsulation efficiency of DOX was determined by ultrafiltration. In vitro release of DOX from PMs were performed using the dialysis method, at pH 7.4 (physiological pH) and 5.0 (tumor acidic pH) for 24 h. Results and discussion: PMs had an average hydrodynamic diameter of 13.5 ± 0.7 nm (n = 3) and zeta potential of -2.9 ± 1.1 mV (n = 3). Zeta potential was neutral due to the presence of PEG in the micelles corona. The CMC was 1.65 x 10^-11 mol L^-1. The low CMC value ensures the stability of the PMs in the blood circulation even after they are significantly diluted. The encapsulation efficiency was 85.3 ± 6.0 % (n = 5). In 24 hours, the PMs released about 25% of loaded DOX at pH 7.4 and 65% of loaded DOX at pH 5.0. It is important that the amount of DOX released is low at pH 7.4 to avoid its side effects and is high at pH 5.0 to try to improve drug delivery to cancer cells. Conclusions: The developed MPs presented suitable characteristics for intravenous application and a pH-dependent drug release. These results indicate that PMs have a potential for enhancing tumor delivery of DOX.

Funding: CNPq, FAPEMIG, CAPES
FORMULATION AND PHYSICAL CHARACTERIZATION OF A NON-IONIC CREAM CONTAINING EXTRACT OF Pereskia aculeata Miller LEAVES

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Introduction: The use of medicines based on medicinal plants is growing in Brazil, especially after the expansion of the therapeutic options offered to the users of the Unified Health System (SUS) including phytotherapics and phytotherapy. Pereskia aculeata Mill. also known as ora-pro-nobis, is a cactus traditionally used for alimentary and medicinal purposes and to this specie are attributed wound healing action. In this context, the aim of the present work was to prepare and to characterize a non-ionic cream containing the crude extract of the leaves of P. aculeata (5% w/w).

Methodology: The extract was obtained by maceration and percolation in alcohol 98.2º GL, concentrated by rotaevaporation and dried by lyophilization. The extract was incorporated into nonionic base cream (Polawax®; 15% w/w). The pure base and the cream were characterized regarding appearence, emulsion type, firmness, cohesiveness and spreadability. The pH and phase separation after centrifugation and thermal stress were studied on days 1, 7, 15 and 30, in products stored under ambient conditions and under refrigeration.

Results and discussion: Smooth, shiny, lump-free formulations were obtained. After the extract incorporation in the base, the cream showed homogeneous color green. Evaluation by optical microscopy and dye test indicated that the emulsion formed was O/A type. There was no phase separation in the samples submitted to centrifugation and thermal stress after preparation and in the storage time studied. The incorporation of the extract did not alter the pH of the product in both conditions tested during the studied period. The incorporation of the extract in the base caused reduction in the firmness and the adhesiveness and, it increased the spreadability of the product.

Conclusion: The proposed formulation presented adequate pharmaceutics parameters for the proposed use.

DESIGN OF EXPERIMENTS (DOE) TO OPTIMIZE a-CYANO-4-HYDROXYCINNAMIC ACID ANCAPSULATION INTO POLYMERIC NANOPARTICLES

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Introduction: Sustained and safe delivery of drugs is highly important to achieve therapeutic success. a-cyano-4-hydroxycinnamic acid (CHC) was previously reported to have therapeutic effect against tumor cells. However, CHC presents limited solubility in addition to stability problems, what can compromise its efficacy. Herein, CHC loaded nanoparticles (NPs) of alginate (ALG) and chitosan (OCS) was developed to be future administered by the nasal route. Methods: NPs ALG/OCS were prepared using modified nanoprecipitation method. A full factorial design were used to analyze the impact of different variables (stabilizing agents, temperature, stirring speed and CHC concentration) on size, zeta potential (ZP), polydispersity index (PDI) and encapsulation efficiency (EE). Size, PDI and ZP were evaluated using Zetasizer nano ZS equipment. The amount of CHC encapsulated by the NPs was determined using UV-VIS spectroscopy. Stability studies were conducted by the periodic analysis of size, PDI and ZP. Results and discussion: Systems with smaller particle size, low PDI, ZP values between +30 to +50mV and high EE% was produced using a stirring speed of 1500 rpm, temperature of 50 °C, Pluronic 188 as stabilizer agent and 2 mg /mL of CHC. CHC loaded NPs provided a size and PDI reduction. In addition, reduction of ZP values between NPs and CHC loaded_NPs evidences the effective encapsulation of the drug. Periodical analysis of size, PDI and ZP demonstrated that NPs showed a good physical stability. Conclusion: This study can be considered as a starting point for the use of ALG/OCS NPs as a promising platform to promote CHC encapsulation.

Acknowledgements: FAPESP

References:
MUCUS DIFFUSING POLYETHYLENE GLYCOL AND HYALURONIC ACID-MODIFIED LIPOPLEXES FOR siRNA DELIVERY TO THE LUNGS

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Introduction: The challenge for siRNA delivery is the development of an efficient carrier. Pegylated mucus-penetrating nanoparticles are known for their capacity to reach the epithelial cells underneath the mucus layer. Moreover, hyaluronic acid (HA) vectorization enables targeting of CD44 receptors, which are transmembrane receptors, found overexpressed in tumor cells. This study aimed at developing HA-lipoplexes modified with PEG coverage for the delivery of siRNA to the lungs. Methods: HA-liposomes were prepared with DOPE and DOTAP lipids by the ethanol injection method. DPPE-PEG 5000 post-insertion was carried out in sequence. Lipoplexes were prepared by mixing liposomes to siRNA solutions in charge ratios of DOTAP (+)/siRNA (−) 2:1; 4:1 and 8:1. Lipoplexes mean diameter, polydispersity index (PdI), zeta potential analyses and mean square displacement (MSD) in airway mucus of healthy patients was evaluated. Results and discussion: Plain lipoplexes were almost completely immobilized, with 90% of nanoparticles showing negative movements and zeta potential of +58 mV, whereas PEG modified HA-lipoplexes showed increased diffusivity up to 100% of positive movements with PEG molar percentage of 12%, and reduced zeta potential of +15 mV with a charge ratio (+/−) 8:1. 10% PEG HA-lipoplexes showed very similar behavior with 99% of positive movements and zeta potential of +14 mV. Conclusion: Effective surface coverage of nanoparticles is crucial for their ability to cross biologic barriers such as mucus, especially lipoplexes, which have high positive charge surface and can interact with mucus components. Surface modification with HA and PEG efficiently improved lipoplexes diffusivity in mucus.

DEVELOPMENT OF NANOSTRUCTURED LIPID CARRIERS BASED ON BEESWAX AND GRAPE SEED OIL FOR TOPICAL DRUG DELIVERY

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Introduction: Beeswax has protective and humectants properties that have been used for centuries as the basis of Cold Cream. Grape seed oil has been shown to have anti-inflammatory and antimicrobial properties. Properly handled, beeswax and grape seed oil may result in a single delivery system with promising properties for the treatment of atopic dermatitis. The aim of this work was to develop nanostructured lipid carriers (NCLs) based on these substances aiming to modulate the barrier function of compromised skins and serve as a carrier for lipophilic drugs used in the treatment of skin diseases. Methods: NCLs were prepared by melt-emulsification coupled with low frequency ultrasound by deploying a quality by design approach. Optimized NCL was characterized by thermal analyzes, morphology, particle size, polydispersity index, zeta potential, conductivity, physical stability, skin resistivity, and skin oil content. Using BODIPY as a lipophilic model and to label the particles, in vitro skin permeation using membrane animal skin and keratinocyte (HACAT) and fibroblast (3T3) assays were performed. Results and discussion: NCL exhibited particle size of 154±1, Pdl of 0.21±0.02, zeta potential of 48±2 and recrystallization index of 6%. These characteristics were maintained for at least 60 days. NCL increased the penetration of BODIPY to deep skin layers, improved the skin lipid content, and did not change its resistivity. They were not cytotoxic and showed a cellular uptake greater than 85%. Conclusion: In conclusion, beeswax/grape seed oil NCL developed showed to be a promising formulation to recover the lipids of compromised skin and to target lipophilic drugs to deep skin layers. Financial support: INCT-NANOFARMA (CAPES #465687/2014-8) and FAPESP (#2014/22451-7)
DEVELOPMENT AND EVALUATION OF STABILITY OF HECOGENIN ACETATE LIPOSOMES

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Introduction: Hecogenin is a steroidal sapogenin commonly found in the leaves of species from Agave genus. Steroids, such as hecogenin, have been used by the pharmaceutical industry in the manufacture of oral contraceptives and other steroid hormones used in clinical treatments. Moreover, hecogenin acetate (HA) is a steroidal acetylated-sapogenin that has important antioxidant, analgesic and anti-cancer properties. However, HA presents low solubility in water and low stability, which limits its use. Liposomes comprising biocompatible lipids are promising nanoparticulate delivery systems, which may increase the solubility and stability of compounds. Thus, in this present study HA-containing liposomes were obtained and their stability was evaluated. Methods: For the preparation of the liposome, phosphatidylcholine, AH and chloroform were added in a volumetric flask, subjected to ultrasound and subsequently to the rotavaporator. After formation of the lipid film, distilled water was added to suspend the film. Thereon, it was submitted to ultraturrax. Size distribution, zeta potential and pH of liposomes were determined at day 1 and 15. Chromatographic analysis was performed by High Performance Liquid Chromatography (HPLC) and entrapment efficiency of liposomes at day 1 and 15 were determined. Results and discussion: The size distribution, zeta potential, pH and entrapment efficiency of liposomes presented appropriate values at the 1st and 15th day, demonstrating stability on this period. The liposomes at the 30th day were not analysed, considering that it presented phase separation. Conclusions: The liposomes demonstrated stability at the period of the study (day 1 to 15) and can be used in future studies. Financial support: The authors are grateful to CAPES and CNPQ for financial support and fellowships.

COMPUTATIONAL AND EXPERIMENTAL APPROACHES TO EVALUATE THE EFFECTS OF PH ON PRECIPITATION BEHAVIOUR OF 5-AMINOSALICYLIC ACID

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Introduction: Saturate solutions are thermodynamically unstable and precipitation may be favoured under physiological conditions, leading to variations in the drug release profile, especially for formulations with high drug loads. Precipitation can generate particles of different shapes and sizes due to different types of interactions between molecules. The structure, properties and formation dynamics of particles in a physiological environment depend on supramolecular interactions. Methods: In this study, computational and experimental approaches (DLS, DSC) were used to evaluate the precipitation behaviour of 5-aminosalicylic acid (5-ASA) as function of pH. Molecular simulation indicated that 5-ASA showed a tendency to precipitate in the pH range of 1–7.5. The pH values 1.5, 4.5 and 6.5 were selected for sample preparation. Results and discussion: Molecular simulation indicated that 5-ASA showed a tendency to precipitate in the pH range of 1–7.5. The pH values 1.5, 4.5 and 6.5 were selected for sample preparation. At a pH of 4.5, 95% of the sample species are zwitterionic; at a pH of 1.5, approximately 76% of the species are in the cationic form; and at a pH of 6.2, the predominant form is anionic (63%). Precipitate formation was observed under these three conditions. The DSC revealed different fusion energy for samples prepared at the three aforementioned pH values. Conclusions: These results were essential for understanding the effect of pH variation on the precipitation of 5-ASA. These findings may also be useful for designing pH-dependent drug formulations and improving methods to predict drug release. Acknowledgments: FAPESP, CAPES, CNPq and INCT.
INTRANASAL DELIVERY OF KAEMPFEROL-LOADED MUCOADHESIVE NANOEMULSION FOR TREATMENT OF GLIOMA

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Introduction: Kaempferol (KPF) is a flavonoid with several pharmacological properties, among them we can highlight the activity against glioma. Recently, the use of nanotechnology has been a promising approach for intranasal delivery to the brain. In this context, this study aimed to prepare nanoemulsions containing KPF with and without chitosan to investigate their potential for brain delivery following intranasal administration, and to evaluate their antitumor activity against glioma cells. Methods: KPF-loaded nanoemulsion (KPF-NE) and KPF-loaded mucoadhesive nanoemulsion (KPF-MNE) were prepared by high-pressure homogenization technique and were characterized for their globule size, zeta potential, drug content, viscosity and mucoadhesive strength. Permeation studies were also performed through the nasal mucosa, as well as the cerebral quantification of KPF after intranasal administration of developed formulations in rats. Finally, activity against glioma cells was assessed. Results and discussion: Both formulations had a nanometric size, low polydispersity index, negative zeta potential for KPF-NE and positive for KPF-MNE and KPF content greater than 96%. Higher mucoadhesive strength was observed for the chitosan-containing formulation as well as increased permeation through the nasal mucosa. In addition, intranasal administration of KPF-MNE increased the KPF content in rats’ brain compared to KPF-NE and free KPF. KPF-MNE showed cytotoxic activity against glioma cells superior to KPF-NE, with induction of apoptosis. Conclusions: KPF-MNE may be a promising system for delivery to the brain, and is a candidate for further antiangioma trials.

Ethical approval: Animal experiments were conducted with prior approval from the Ethical Committee of the Federal University of Rio Grande do Sul (Protocol # 31216).

Financial support: This work was supported by CNPq and CAPES/MEC.

“IN VITRO” BIOLOGICAL AND BIOPHARMACEUTICAL EVALUATION OF THE INCLUSION COMPLEXES OF THE ANTIFUNGAL COMPOUND 2-(2-NITROVINYL)FURAN WITH BETA- CYCLODEXTRIN DERIVATIVES

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Introduction: 2-(2-nitrovinyl)furan (G-0) has antifungal activity, but limited stability. Inclusion complexes with beta_CD derivatives are alternatives to solve this problem. The aim of this work was to evaluate their influence on the dissolution profile, permeability and cytotoxicity of the drug. Methods: Dissolution studies of pure drug, physical mixtures (PM), kneaded (KM) and freeze-dried (FD) complexes were carried out using USP dissolution apparatus I. Dissolution efficiency (DE) was calculated from the release curves. Permeability through cellulose acetate membrane and bovine vaginal mucosa were performed using Franz Cell Diffusion Chamber. Samples were dispersed in SVF and the receptor was PBS solution. Cumulative drug release per area unit were plotted. Citotoxicity of cyclodextrins, G-0 and FD complexes was tested against L929 and HaCaT cell lines using the MTT assay. CC₅₀ was calculated by non-linear concentration/response regression model. Results: KM, FD complexes and PM improved the dissolution rate of G-0. %DE₃₀ min following the ranking order: G-0 < PM G-0/SBEbeta_CD < PM G-0/HPbeta_CD < KM G-0/HPbeta_CD < KM G-0/SBEbeta_CD < FD G-0/HPbeta_CD < FD G-0/SBEbeta_CD. About 50% of drug permeated through cellulose acetate membrane but not through bovine vaginal mucosa. Penetration experiment showed some retention in the mucosal tissue for all the samples without statistical differences between them (p>0.05). CC₅₀ determined for pure G-0 were 43.72µM in L929 and 21.33µM in HaCaT. Both inclusion complexes increased CC₅₀ values, being higher for FD G-0/SBEbetaCD for both cell lines (155.59 and 78.60µM). Conclusions: FD inclusion complexes have fast dissolution, moderate retention in vaginal mucosa and less cytotoxicity than pure drug.

Acknowledges: The authors would like to thank to the AUIP organization for grant the doctoral financial aid and to the Chemical Bioactives Center from Cuba, for providing the drug candidate (G-0) used in this work.
DEVELOPMENT OF A THERMOSENSITIVE LIPOSOMAL FORMULATION FUNCTIONALIZED WITH HYALURONIC ACID

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Introduction: Thermosensitive liposomes (TL) are clinically relevant nanocarriers used to deliver chemotherapeutic agents in combination with local hyperthermia¹. The association of hyaluronic acid (HA) and TL might be used as a strategy for delivering anticancer drugs to targeted tissue². Thus, the aim of this study was to develop a new TL functionalized with HA for further application in tumor therapy. Methods: The TL were developed by the lipid film hydration method and extruded through polycarbonate membranes. The influence of the lipid concentration on the physicochemical characteristics of the liposome was evaluated by dynamic light scattering. Liposomes were incubated with HA solution at different concentrations (0.05 to 9.0mg/ml) for functionalization. Furthermore, thermosensitivity preliminary study was performed to evaluate the effects of temperature on the liposomal vesicles. Results and discussion: The variation in lipid composition did not alter the size of the liposomes (190-210 nm) or the zeta potential (+30 to +40 mV). Functionalization with HA was confirmed by zeta potential measurements, whose values reached -30mV. However, an increase in mean diameter was observed after HA functionalization, obtaining a mean diameter of 450-500 nm. The results of the thermal analysis indicated that thermosensitivity at 40 °C, however additional studies of DSC are needed to confirm this result. Conclusion: Liposomes were successfully prepared, showing suitable physicochemical characteristics. The functionalization with HA through electrostatic interaction was efficient and confirmed by zeta potential. In addition, preliminary studies of thermosensitivity showed promising results indicating this formulation as a potential system for delivering antitumor drugs.

NOVEL NANOSTRUCTURED LIPID CARRIER CO-LOADED WITH DOXORUBICIN, DOCOSAHEXAENOIC ACID AND α-TOCOPHEROL SUCCINATE FOR CANCER THERAPY

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Introduction: Doxorubicin (DOX), an anthracycline with a broad-spectrum of anticancer activity, is widely used in cancer therapy. The combination of docosahexaenoic acid (DHA) or α-tocopherol succinate (TS) with DOX has been described as an alternative to increase antitumor efficacy. Therefore, this work aims to develop and characterize a novel nanostructured lipid carrier (NLC) co-loaded with DOX, DHA and TS (NLC-DOX-DHA-TS) for cancer therapy. Methods: NLC-DOX-DHA-TS were prepared by hot melting homogenization method and characterized for size, polydispersity index (PI) and zeta potential (ZP). Two strategies were evaluated for DOX encapsulation: the first using the conventional emulsification-ultrasound method and the second incubating DOX with blank NLC (NLC-DHA-TS). The entrapment efficiency (EE) of DOX was evaluated by HPLC. Release studies were conducted by dialysis in PBS buffer using different pH values. Results and discussion: Incorporation of DOX using emulsification-ultrasound method resulted in drug degradation. In contrast, incubating DOX with blank NLC prevented this degradation. The size, PI and ZP of NLC-DOX-DHA-TS was 75 nm, 0.19 and -35 mV, respectively. The EE was high and reached 100%, due to the formation of an ion pairing between DOX and TS, which was characterized by IR and NMR. The release data showed the potential for developed NLC to provide a controlled drug release. At physiological pH, the released DOX from NLC was about 5% after 1 h, and gradually increased to 21% after 24 h. In contrast, at pH 6.8, about 8% of the drug was released after 1 h, and gradually increased to 38% after 24 h. Therefore, drug release in slightly low pH from NLC-DOX-DHA-TS was significantly higher than that observed at physiological pH. Conclusions: NLC-DOX-DHA-TS showed size, PI and ZP adequate for parental administration and a controlled release of DOX. Next steps of this work include the evaluation of the pharmacokinetic profile and the in vivo antitumor activity of this formulation. Acknowledgment: CAPES, FAPEMIG.
OPTIMIZATION OF CHITOSAN-COATED NANOEMULSIONS FOR ROSMARINIC ACID NASAL ADMINISTRATION

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Introduction: Rosmarinic acid (RA) is a natural polyphenolic compound with several biological activities reported, including a well-documented neuroprotective effect. Nevertheless, besides the RA low bioavailability, technological approaches for this compound are quite limited. In this way, the present work aimed to optimize chitosan-coated nanoemulsions for RA nasal administration. Methods: Box-Behnken design (BBD) was chosen to statistically optimize RA chitosan-coated nanoemulsions for three experimental factors (X1: oil phase, % w/v; X2: lecithin to oil phase ratio; X3: chitosan, % w/v) in three factor levels (-1; 0; +1) based on the main effects on droplet size (Y1), polydispersity index (PDI) (Y2), ζ-potential (Y3) and content of RA (Y4). A total of 15 runs in random order were designed. Results and discussion: In summary, the responses value for Y1, Y2, Y3, and Y4 ranges from 270.23 to 448.40 nm, 0.269 to 0.490, 41.97 to 48.63 mV, and 82.72 to 100.79 % of RA, respectively. The suitability of BBD was demonstrated by the high coefficient of determination obtained for all responses (R²=0.9844, 0.9861, 0.8759 and 0.8455, respectively). Furthermore, once no evidence of inadequacy was observed by lack-of-fit, the mathematical models showed to be suitable for the analysis of response surface (p>0.05). The optimal condition for preparation of formulations with minimum droplet size and PDI, and highest ζ-potential and RA content were obtained. Optimized conditions were 8.5% (w/v) oil phase, 3:10 (w:w) lecithin ratio in oil phase, and 0.1% (w/v) chitosan concentration. Conclusions: An optimized chitosan-coated RA nanoemulsion formulation was successfully obtained through a BBD. Acknowledgements: Financial support from CNPq, FAPERGS and grants from CAPES.

POLIMERIC POLY(ETHILENE CARBONATE) NANOPARTICLES FOR THE TREATMENT OF TUBERCULOSIS

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Introduction: Nanotechnology has been applied in the development of new therapeutic strategies, aiming at improving and increasing the possibilities of cure of the targeted diseases. Tuberculosis (TB) is a disease caused by Mycobacterium tuberculosis, an intracellular parasite that mainly affects the lungs, with alveolar macrophages being the main targeted cells. Because it is a serious public health problem and affects millions of people annually, the development of new alternatives that allow effective therapy has been investigated. The development of polymeric nanoparticles enables a controlled release system with the delivery of drugs directly at the site of action, and offers a potential targeting of the drug. Polymers (ethylene carbonate) (PEC) is a biodegradable polymer that has specific degradation by the enzyme cholesterol esterase and macrophages, and can be used in nanoparticles for TB therapy by specific targeting of the drugs to the infected target cell, macrophages. Methods: PEC nanoparticles were obtained by nanoprecipitation for the encapsulation of a tuberculostatic drug, clofazimine (CFZ), which has been used for treating multidrug resistant TB (TB-MDR). Different proportions of sorbitan monooleate (Span80®), polysorbate 80 (Tween80®) and poloxamer 407 (Pluronic F127®) were tested as formulation adjuvants to optimize particle preparation. The best formulations, using Span80® and Pluronic F127® were chosen for further testing due to the small particle size and Pdl. The mean diameter and polydispersity index (Pdi) of the nanoparticles were measured by dynamic light scattering, and encapsulation efficiency (EE) was determined using ultrafiltration and liquid chromatography (HPLC) for CFZ quantification. Results and discussion: The nanoprecipitation method for nanocapsules production presented a process yield of 90%. Particles had a mean diameter of 209 nm, mean Pdl of 0.111 and calculated EE was 65%. The parameters of the spray-drying technique are being optimized for the production of a dry powder containing CFZ for pulmonary administration. Conclusion: Small, homogeneous and CFZ-encapsulating PEC nanoparticles were prepared by the nanoprecipitation method for further characterization and testing, to determine if the administration of the nanoparticle-based treatment directly to the lungs and targeted to the diseased cells may allow a better patient adherence to treatment, reduction of side effects and therapeutic efficacy of the disease.
IN VIVO AND IN VITRO DERMATOPHARMACOKINETICS STUDIES WITH LAPACHOL TOPICAL FORMULATION

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Introduction: The skin as a route of topical drug administration for local or systemic action has been widely used. Considering that Lapachol in gel pharmaceutical form has demonstrated significant anti-inflammatory activity when applied topically, this study proposes to evaluate the behavior of a gelled formulation containing 0.5% of this drug through dermatopharmacokinetics in vivo and in vitro technique which allows drug quantification in the stratum corneum.

Methods: In vitro experiment was performed with pig dorsal skin in automated Franz diffusion apparatus with fourteen replicates for 2 and 6 hours of contact. In vivo study (local ethics committee approval, CAAE 36315514.2.00005208), 14 volunteers participated and the same formulation was in contact with the skin for 2 and 6 hours as in vitro evaluation. The drug was examined through dermatopharmacokinetics, by removal of the stratum corneum with adhesive tapes using tape-stripping technique with subsequent extraction and analysis.

Results and discussion: For the in vitro study, a mean of 1.014 μg/mL and 0.774 μg/mL of lapachol respectively were quantified at 2 and 6 hours in the stratum corneum. The lapachol values obtained for the in vivo study were 0.628 μg/mL for the 2 hours of contact and 0.488 μg/mL for 6 hours. The in vitro and in vivo studies results did not present statistically significant difference (Student’s t-test).

Conclusion: The in vitro/in vivo dermatopharmacokinetic correlation made possible the lapachol evaluation in the stratum corneum and this methodology contributed to the consolidation of effective and safe evaluation of drugs administered topically.

Acknowledgments: The authors would like to thank Coordination for the Improvement of Higher Education Personnel, Brazil- CAPES, Nucleus of Pharmaceutical and Cosmetic Development - NUDFAC and Carlos Drummond de Andrade Pharmacy School - FECDA.

Ethical approval: The study protocol (CCAE 36315514.2.00005208) was approved by local ethics committee of the Federal University of Pernambuco, Recife, Brazil.

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DEVELOPMENT OF MULTILAMELLAR LIPOSOMES CONTAINING LEVOBUPIVACAINA CHLORIDRATE

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Introduction: Pain is a phenomenon that affects the population, mainly people who suffered surgical procedure. The relief of post-operative pain is managed with analgesic medicines. Levobupivacaine hydrochloride is a widely used local-acting drug that promotes long lasting effects. However, cardiotoxicity is one of the adverse effects related to its repeated usage. Therefore, in order to increase the releasing time the goal of this work was to develop a liposome containing levobupivacaine hydrochloride. Methods: Liposomes were prepared using the dried thin lipid hydration method followed by sonication. First, different batches of liposomes loaded with levobupivacaine hydrochloride were prepared using different lipid concentrations (from 42 to 240 mM) and different drug concentration (2 to 5 mg/mL) in order to achieve the best formulation in terms of stability. The formulations were characterized in terms of particle size, polydispersity index (PDI) and zeta potential. The encapsulation efficiency of levobupivacaine hydrochloride into the liposomes was determined by ultracentrifugation/ultrafiltration. Results and discussion: The prepared formulations were stable for 30 days, except the liposomes prepared at 42 mM. Particle size ranged from 334.8 ± 4.17 to 414.33 ± 5.9nm and the polydispersity index was lower than 0.5, suggesting that the systems are homogeneous with a neutral charged’s surface. The drug encapsulation efficiency rate was near to 80%. Conclusion: This work successfully developed liposomes loaded with levobupivacaine hydrochloride and the obtained system was stable according to the characterization results.

Acknowledgments: The authors would like to thank Coordination of Improvement of Higher Education Personne, Brazil- CAPES, the Nucleus of Pharmaceutical and Cosmetic Development- NUDFAC and the Keizo Asami-Lika Immunology Laboratory.
PREPARATION AND CHARACTERIZATION OF INCLUSION COMPLEXES OF PROPOLIS WITH β-CYCLODEXTRIN AND hydroxypropyl-β-cyclodextrin

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Propolis is a natural product derived from plant resins collected by honeybees. The chemical complex composition of propolis includes more than 150 constituents with numerous pharmacological properties. The application of propolis resins in medicine products is restrained by their poor aqueous solubility and bitter taste. CDs are cyclic oligosaccharides made up of α(1-4)-lycosidic-bonded glucopyranose units. These macro-rings have a relatively hydrophobic inner cavity as opposed to the hydrophilic exterior. Inclusion complexation by CDs can provide stabilizing and solubilizing effects on the guest molecules. Among these CDs, βCD and its hydrophilic derivative, hydroxypropyl-β-cyclodextrin (HPβCD), are the first choices because of their suitable cavity sizes. This study aimed at development and characterization of propolis inclusion complexes in βCD and HPβCD. Nano-systems were obtained by addition of propolis’s ethanolic solution in the -β and -HPβCDs in 50ml of ethanol 20%, using mass ratio of 1:1, 1:2, 1:3 and 1:5, under magnetic stirring for 72 hours. After the reaction time, the organic solvent was evaporated using a rotary evaporator and the samples were freeze-dried. The nanosystems were characterized by yield, fourier transformation-infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). The nanosystems with ratio (1:5) were obtained with greater yields (75,58%) and FTIR analysis exhibited characteristic bands of the propolis in this systems (400-3900 cm⁻¹). In the thermal analysis were observed the disappearance of the propolis melt peak (110ºC), indicates the complexation of resin in the CDs. Therefore, these results demonstrated that the solution method was efficient to obtained nanosystems contain propolis.

Acknowledgements: CAPES, CNPq; FAPERJ.


DEVELOPMENT OF NEW ADHESIVE NANOTECHNOLOGY FORMULATION FOR DRUG DELIVERY BASED ON PECTIN

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Introduction: Nanoencapsulation strategy has been used to deliver drugs to the selected sites through many administration routes such as the skin. In order to achieve a high drug delivery through the skin, adhesive formulations should be used. This work aims to characterize and evaluate the skin permeability and adhesiveness of a pectin gel containing polymeric nanocapsules. Imiquimod was used as a model lipophilic drug. Methods: The polymeric nanocapsules suspension was developed by nanoprecipitation and was incorporated into a pectin gel (NanoGel). For comparison, the free drug was dissolved in buffer pH 3.7 and also incorporated into a pectin gel (FreeGel). The polymeric nanocapsules and NanoGel were characterized by laser diffraction and transmission electronic microscopy. The permeability study was performed in automatic Franz diffusion cell, comparing the permeability between NanoGel and FreeGel in porcine skin. The adhesiveness of NanoGel was evaluated in texturometer analyzer. Results and discussion: The polymeric nanocapsules and NanoGel showed nanometric size and spherical characteristic (around 300 nm). After the permeability study, it was possible to verify that NanoGel permeated more than FreeGel, approximately ten times more after 8 and 12 hours and four times more after 24 hours of study. Neither NanoGel nor FreeGel permeated before 6 hours. NanoGel presented higher adhesiveness when compared to FreeGel, and this result may explain the increase in the amount of imiquimod permeated. Conclusions: The pectin gel containing the nanocapsules presented promising results in permeability study, when compared to free drug. This nanogel can be studied for systemic delivery of lipophilic drugs.
PREPARATION AND CHARACTERIZATION OF MICROEMULSION SYSTEMS CONTAINING Melaleuca alternifolia ESSENTIAL OIL

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Melaleuca alternifolia (Myrtaceae) is an australian native tea tree species. Its essential oil has been widely used in modern medicine in recent years, incorporated into new drug delivery system, like microemulsions (ME), by present antimicrobial, anti-inflammatory and healing action. The aim of this study was to develop and characterize a ME systems containing Melaleuca alternifolia essential oil (MEO). Hydrophilic-lipophilic balance of the three components [isopropyl myristate, Kolliphor® HS 15/Span® 80 (9:1)] and deionized water, as aqueous phase, were employed to obtain the pseudoternary phase diagram. The point chosen to conduct the study followed the requirements stipulated: to be a semi-solid and viscous system maintaining its stability conditions up to 48 hours post-production. MEO was incorporated into ME (MEO-ME) in the selected formulation (3.45% v/v). Next, the MEO-free ME and MEO-ME systems were characterized using polarized light microscopy, pH and rheology techniques. The samples were considered as microemulsions, since they cannot deflect the plane of polarized light (acting as isotropic systems). The pH of the systems 6.63 and 6.73 for MEO-free ME and MEO-ME, respectively, are compatible with the skin, making it suitable for topical administration. In rheology, the samples were characterized as a non-Newtonian pseudoplastic fluid with thixotropy, thus allowing an efficient skin bioadhesion. Therefore, MEO-ME system present itself as a feasible for application by the topical route.

MICROEMULSION AS A TOPICAL DELIVERY SYSTEM FOR DEXAMETHASONE

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Dexamethasone (DEXA) is a glucocorticoid drug with anti-inflammatory activity. Its continuous use in systemic and/or topical form causes undesirable effects. And microemulsions (MEs) are potential drug delivery systems that can transport pharmaceuticals compounds decreasing the incidence of adverse drug reaction. The objective of this study was to develop and characterize a microemulsion system for topical delivery of DEXA. The system was produced with the construction of the pseudoternary phase diagram, using Labrasol®/Brij® 52 (9:1), as surfactants, isopropyl myristate, as oil phase, and deionized water, as aqueous phase. A formulation was selected and DEXA incorporated at the concentration of 0.1% (w/w). This system was characterized by macroscopic appearance, pH, electrical conductivity, refractive index (RI), average droplet size (ADS), polydispersity index (PDI), zeta potential (ZP), and encapsulation efficiency (EE). Macroscopically the system presented as liquid, transparent, and homogeneous. Its pH (5.00 ± 0.03) shows that the system is suitable for topical use. It presented electrical conductivity of 101.60 ± 1.9 μS/cm, indicating that this system is O/W type, and constant RI of 1.369 ± 0.0. Its ADS was 16.03 ± 0.12 nm with PDI of 0.0678 ± 0.31 being in accordance with that proposed for MEs with a monomodal size. It presents a negative ZP (-23.14 ± 0.46 mV), what favors the stability of the system, and an excellent EE (100% ± 3.52). Therefore, it can be concluded the microemulsion system was able to incorporate DEXA effectively, presenting itself as an alternative for the topical anti-inflammatory treatment.
EQUIVALENCE STUDY OF THREE COMMERCIAL FORMULATIONS OF DEXAMETHASONE ACETATE CREAMS

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Some recommended tests can evaluate the quality of the formulations under biopharmaceutical aspects, assuming that the registered medicines will have the same efficacy and safety. In this way, they will be able to show the interchangeability or not between the reference medicines with similar and generic ones. Among the dermatological creams intended for surface application to the skin, dexamethasone acetate (DA) is one of the most commonly used glucocorticoids in the clinic. The objective of this study was to evaluate the equivalence among three DA creams (reference, generic and similar). These different DA creams (1.0 mg/g) were evaluated for pH, spreadability, and centrifugation test, and in vitro release profile by Franz diffusion cell system. The creams presented pH within the required specifications, around 5.0 $\pm$ 0.6 and centrifugation test without indicative of instability. The in vitro release study followed the Higuchi kinetic model for the three formulations with correlation coefficient values above 0.99. The generic cream presented a lag time of release and greater spread profile among the formulations. The similar cream presented lower flow and percentage of release, what is explained by the smaller amount of permeation promoters in its composition and probable affinity between the drug and the excipients of the formulation. Therefore, in spite of the small differences between the formulations, generic and similar DA creams were considered equivalent to the reference for the release of the active, as evidenced by the statistical analysis of the non-parametric method Wilcoxon Rank Sum/Mann-Whitney.

INFLUENCE OF SPRAY DRYER VARIABLES IN MORPHOLOGY OF ALGINATE MICROPARTICLES CONTAINING INDOMETACIN

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Microparticulate release systems with the use of polymers become a viable option for the incorporation of drugs such as indomethacin (IND). One of the factors that influence the release of drug is the morphology of microparticles (MP). This work aimed to evaluate the variables that influenced the morphology of alginate MP with the incorporation of IND. To obtain the microparticles suitable for the study, an experimental design was performed, where previously evaluated parameters were kept fixed. Alginate solutions (2%) were sprinkled using a spray dryer with the following drying parameters: the peristaltic pump with flow of 0.3 L/h, outlet temperature (75 °C), compressed air flow were kept fixed (40 L/min), while the drying air flow rate (3.5 and 4.5 m$^3$/min) was varied. In the preparation of the systems, the polymer concentration (2%) was maintained while the co-solvent used for IND incorporation was varied (INDMP1: ethanol; INDMP2: propylene glycol). To evaluate the morphology of MP, Scanning Electron Microscopy (SEM) was used. Photomicroscopies showed that IND-free MP in different airflow rates presented similar morphology. However, with the presence of the drug, it was observed that INDMP2 and airflow of 4.5 m$^3$/min showed better results with a more spherical shape, uniform sizes and no free drug. Thus, through the study it is possible to observe the importance of the independent variables in the process of obtaining a new MP.
MOLECULAR MODELING AND MOLECULAR DYNAMICS SIMULATIONS OF MOLECULAR SYSTEMS CONTAINING POLYMERS AND ANTITHROMBOTIC N-ACYLHYDRAZONE DERIVATIVES

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Platelet aggregation is one of the major precursors of cardiovascular accidents and is one of the main events involved in these thrombotic disorders. Moreover, antiplatelet agents available on the market have severe adverse effects on the health of the patient, especially bleeding and recurrent lesions of the unsatisfactory pharmacokinetics, then the development of drug delivery systems may allow superior therapeutic efficacy to conventional formulations. The nanoparticles can be prepared using different materials, of which the polymers are one of the most applied drug carriers. Thus, the main objective of the present work was to study the molecular systems containing poly(lactic-co-glycolic acid) (PLGA) or polycaprolactone (PCL) and compound 2C, an antithrombotic N-acylhydrazone derivative, applying molecular dynamics simulations. The three-dimensional molecular structures of compound 2C and both polymers monomers were constructed and optimized using the Spartan’10 program. Following the geometry optimization, the polymers chains were increased and added in an initial amorphous cell. Then, the simulation boxes with dimensions 12x12x12 nm³ were prepared in order to insert polymers molecules containing 60 monomers each and 2C molecules at water medium (Xenoview program). The molecular dynamics were performed. The PLGA molecules showed more affinity to 2C molecules than PCL chains. The PLGA molecules dispersed in the aqueous medium interacting with the 2C molecules, while the PCL molecules remained bound together forming a nanoparticle rapidly without influence on the 2C molecules dissolution in water environment. The molecular dynamics simulations results indicated the PLGA as a more favorable polymer to development of nanoparticles containing compound 2C.

STRESS DEGRADATION STUDY OF AN ISOLATED PHOLOROGLUCINOL OF Eugenia umbelliflora (Myrtaceae)

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Introduction: Phloroglucinol is an important class of bioactive secondary metabolites isolated from different natural sources. From the green fruits of Eugenia umbelliflora, it was isolated five pholoroglucinols by our research group. Among them, eugenial C presents an important antibacterial activity against MRSA strains and cytotoxicity against leukemia cells. Eugenial C is a potential drug candidate it is necessary to determine its stability. Objective: This works aims to study the in silico and in vitro stability of eugenial C. Methods: Eugenial C was isolated, purified and submitted to stress degradation tests (acid and alkaline hydrolysis, oxidation, visible/UV radiation and dry/humid heating) monitored by LC-UV, LC-MS and NMR ¹H and ¹³C analysis. In addition the molecule was submitted to in silico approaches, to predict the more susceptible regions in the structure to degradation. Results and discussion: Eugenial C showed > 90% of purity, being sparingly soluble in methanol, slightly soluble in acetonitrile and practically insoluble in water and gastric fluid pH 1.2. In silico studies indicated the regions of greater susceptibility to acid, basic and oxidative hydrolysis, comproved by in vitro stress test, revealing that is extremely unstable in acid, basic and oxidative conditions. A heated sample showed the rupture of the double bond at the C10 ‘o of the cycloheptane, this may have happened due to an oxidation reaction as predicted by in silico studies. Conclusion: The results point out the susceptibility of eugenial C to degradation conditions and the need to develop a protective drug release system for this potential phytodrug.
DIFFERENTIAL SCANNING MICROCALORIMETRY AND CIRCULAR DICHROISM STUDIES OF BEVACIZUMAB IN NANOCOMPLEXES BASED ON GELLAN GUM/RETROGRADED STARCH BLENDS

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Introduction: The carrying of protein drugs as bevacizumab (BVZ) in mucoadhesive nanocomplexes (nanoPECs) prepared via polyelectrolyte complexation is a promising technological strategy to protect this bioactive molecule against degradation, modulating its release rates throughout the gastrointestinal tract. Additionally, the targeting of BVZ to colon can improve the biological interaction with tumor tissue, regarding the localized therapy of colonic cancer. The keeping of protein structural integrity is crucial to assure its biological activities at the site of absorption/action. Methods: NanoPECs based on gellan gum/retrograded starch containing BVZ were prepared by polyelectrolyte complexation. Cross-linked nanoPECs were prepared by further ionic cross-linking with aluminum chloride (Al³⁺). Structural conformation of BVZ was evaluated by Differential scanning microcalorimetry (Nano-DSC) and Circular dichroism (CD) analysis. Results and discussion: Nano-DSC measurements revealed two thermal denaturation events of BVZ at 70 °C and 80 °C, relative to the melting of Fab and Fc fragments, respectively. For both nanoPECs and cross-linked nanoPECs, the thermal denaturation of BVZ occurred at high temperatures (~100 °C). CD analysis showed that BVZ secondary structure was kept after the preparation process, and even after incubation of nanoPECs and cross-linked nanoPECs in 0.1 M phosphate buffer pH 6.8, during 240 min. Conclusion: Nanocomplexes based on gellan gum/retrograded starch blends containing BVZ were successfully prepared by polyelectrolytic complexation and ionic cross-linking techniques. The carrying of BVZ in such structures increased its thermal stability. The preparation process of nanoPECs and cross-linked nanoPECs do not change the structural conformation of BVZ. Acknowledgments: FAPESP, CAPES, INCT.

COMPATIBILITY STUDY BETWEEN N-ACYLHYDRAZONIC DERIVATIVE AND CHITOSAN IN FORM OF FILMS

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The combination of N’-(3-(1H-indol-3-yl) benzylene)-2-cyanoacetohydrazide (JR19) with chitosan (CHI) in the form of films is presented as an innovative proposal in the treatment of cutaneous inflammations, since the drug expressed anti-inflammatory activity in vivo studies. The objective of this research was to identify the functional groups, which can determine the presence of CHI and JR19 in the developed films, through the technique of Fourier Transform Infrared Spectroscopy (FTIR). This analysis was performed using a Spectrum 400 Perkin Elmer® FTIR/FTNIR Spectrometer, in the range between 4000 and 650 cm⁻¹. Infra-red spectra showed bands characteristic of the main functional groups of the molecule JR19 and CHI, such as the detection of the nitrile (CN) band, which ranged from 2255 to 2289 cm⁻¹ and the amide carbonyl bands between 1641 and 1728 cm⁻¹. These signals are common to the chemical structure of JR19, then verified in the isolated molecule, physical mixture of CHI-JR19 (1:1 w/w) and CHI-JR19 film. In the region between 3500 and 3200 cm⁻¹, it was possible to observe absorptions suggestive of stretching vibrations of O-H and/or N-H bonds of CHI. CHI-JR19 film showed absorption bands in this same region what can also be attributed to the N-H bond of the indole group of the molecule. Hence, it is concluded that the CHI-JR19 films presented characteristics of both the functional groups of CHI and the molecule in study, due to the appearance of absorption bands in the same signal range of the isolated samples.
**COMPATIBILITY STUDY BETWEEN INDOMETHACIN+CHITOSAN IN LYOPHILIZED SPONGES**

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Indomethacin (IND) is an anti-inflammatory, antipyretic and analgesic drug that has shown good results for the treatment of lesions when incorporated into chitosan (CHI) devices, such as lyophilized sponges. Chitosan is a polymer obtained from alkaline deacetylation of chitin, its biological properties are motivating in the scientific field, mainly biodegradability and biocompatibility. The objective of this study was to evaluate the compatibility between the IND and the CHI using the differential scanning calorimetry (DSC). Samples of CHI and IND were used in their isolated forms, in addition to IND-free CHI and IND into CHI lyophilized sponges. The calorimetric curves were obtained in a differential exploratory calorimeter module model DSC Q20 (TA® Instruments) with a 10°C min⁻¹ heating rate in the temperature range 25–400°C under a dynamic nitrogen atmosphere (50 mL min⁻¹) and 2.00±0.05 mg mass. The DSC curve of the IND showed an endothermic peak ($T_{\text{peak}}=162.01$°C and $\Delta H=195.9$ J.g⁻¹), relative to drug fusion. The CHI powder had two peaks, one endothermic ($T_{\text{peak}}=142.02$°C and $\Delta H=211$ J.g⁻¹) and another exothermic ($T_{\text{peak}}=306.42$°C and $\Delta H=187.6$ J.g⁻¹) that were also observed in the IND-free CHI sponge. The IND into CHI sponge presented the following thermal events, one endothermic with $T_{\text{peak}}=131.62$°C and $\Delta H=277.62$ J.g⁻¹ and another exothermic with $T_{\text{peak}}=299.09$°C and $\Delta H=86.55$ J.g⁻¹. The data suggest characteristics of incompatibility between the drug and the polymer matrix, due to the disappearance of the characteristic endothermic peak of indomethacin. Thus, it is observed the importance of this thermoanalytical technique for the development of a new formulation.

**PEGYLATED CATALASE AS A POTENTIAL BIOBETTER FOR THE VITILIGO TREATMENT**

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Catalase (CAT) is an important antioxidant enzyme that catalyses hydrogen peroxide decomposition. Recently, catalase has been suggested as potential molecule to treat vitiligo. Patients with vitiligo have low catalase levels in their epidermis in association with high levels of free radicals. This free radicals accumulation result in oxidative stress which has been demonstrated in the pathogenesis of vitiligo. For this reason, topical use of catalase in association with UV therapy has been suggested as a new treatment modality. Considering that, we investigated the PEGylation of catalase as a potential biobetter with enhanced long-term stability and increased bioavailability. In order to define an optimal site-specific PEGylation protocol, different pH values were tested for PEGs with 10, 20 and 40 kDa. PEGylation yields of 45%, 59% and 31% for CAT-PEG-10, CAT-PEG-20 and CAT-PEG-40 respectively were obtained. Purification of the PEGylated proteins was carried out by FPLC-SEC and the molecular weight of purified enzymes analysed by native electrophoresis. Protein structural studies were achieved through circular dichroism, showing that PEG coupling did not compromise the secondary and tertiary structure of the catalase. Moreover, thermal stability assays showed that both CAT and the CAT-PEG variants exhibit a higher aptitude to resist to thermal denaturation ($T_m = 65$°C). The peroxidative activity was also measured and PEG binding to the protein caused a considerable decrease in peroxidative activity (13% for CAT-PEG-10 and 45% for CAT-PEG-20 and CAT-PEG-40). Further experiments will be carried out to confirm CAT-PEG variants stability over the time and on skin samples. 

**Acknowledgements:** The authors are grateful for the financial support of CAPES, CNPq, FAPESP (2016/22065-5) and the Foundation of Science and Technology (FCT - Portugal) for the doctorate of SFRH / BD / 102915/2014 to João HPM Santos.
**INNOVATIVE NANOTECHNOLOGICAL SEMISOLID FORMULATION WITH NC-Phl - DEVELOPMENT AND CHARACTERIZATION**

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**Introduction:** Biological properties of flavonoid phloretin include antioxidant capacity, anticancer action, among others. However, its poor solubility in water (0.040 ± 0.002 mg/mL) impairs the incorporation into hydrogel for topical use. The aim of the present work was the development of an innovative semisolid formulation (HG-NC-Phl) containing polymeric nanocapsules with phloretin (NC-Phl). Similarly, a semisolid formulation with phloretin not encapsulated has also been developed and characterized (HG-Phl). Methods: The NC-Phl suspension, previously developed and characterized, containing 0.2 mg/mL of phloretin, was used to produce the gel (HG-NC-Phl). Laser diffraction technique was chosen to analyze the presence of nanoparticles. pH measurement was obtained by potentiometry after dilution of the formulation into ultrapure water (1:10 w:v) in triplicate. For viscosity evaluation, we employed rotational viscosimeter with the spindle SC4-25 at 25°C. Scanning electron microscopy was also performed in order to verify the presence of nanoparticles. All analyses were compared with the free phloretin gel (HG-Phl), obtained by phloretin dispersion in polysorbate 80, incorporated in water and thickened with the phospholipid-based gelling agent.

**Results and discussion:** The suspension of polymeric nanocapsules-loaded Phl showed nanometric diameter (202.55±6.58) and low polydispersity index (0.11±0.03). In addition, it was found that 100% of the drug was encapsulated. The HG-NC-Phl showed nanometric population, this means that after the production of the hydrogel the polymeric nanocapsules remained intact. HG-Phl showed particle size distribution in the micrometric band, close to 202µm. Scanning electron microscopy images demonstrated the integrity of nanocapsules in HG-NC-Phl. The pH of gels was 6.73±0.04 and 7.20±0.10 for HG-NC-Phl and HG-Phl, respectively. The viscosity of HG-NC-Phl was inferior to HG-Phl. Conclusions: The innovative nanotechnological gel containing phloretin has been successfully developed and it shows a promising strategy for topical application of the antioxidant molecule.

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**Aniba canelilla (H.B.K.) MEZ ESSENTIAL OIL: DEVELOPMENT OF TOPICAL NANOEMULSION AND HYDROGEL-THICKENED NANOEMULSION, CHALLENGES ON THE SKIN PERMEATION ASSAYS AND ASSESSMENT OF ANTI-INFLAMMATORY ACTIVITY**

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**Introduction:** The essential oil extracted from Aniba canelilla (H.B.K.) Mez, an aromatic plant from Amazon, has 1-nitro-2-phenylethane (NP) and methyleugenol (ME) as major compounds and presents anti-inflammatory activity. The oil imparts an unpleasant feel when used topically and its nanoemulsification may confer benefits concerning stabilization, penetration and activity to treat locally inflamed skin. Methods: HS-SPME-GC-FID bio/analytical validations were performed for NP and ME assay. A nanoemulsion (NE) and a hydroxyethylcellulose-hydrogel-thickened nanoemulsion (HNE) containing the essential oil (EO) were prepared and characterized for markers content, droplet size, zeta potential, and polydispersity index. Permeation studies were performed for EO, NE and HNE using Franz diffusion cells. Anti-inflammatory activity was also assessed by croton oil-induced ear edema in Swiss mice.

**Results and discussion:** A validated GC method that requires data linearization (Log $X$-Log $Y$) allowed quantifying NP and ME directly in skin matrix and formulations. NE and HNE presented low droplet size (< 147.06 nm) and polydispersity index (following order: stratum corneum<epidermis<dermis<receptor fluid. Inflammation inhibitory effects of positive control (dexamethasone) presented no statistical difference towards NE, whereas statistical difference was observed to EO and HNE, due to a slower release of markers from the nanosystem when entrapped in the hydrogel. Conclusions: The high retention and permeation of the volatile compounds in the skin and the maintenance of the anti-inflammatory activity open perspectives for NE use to topical treat inflammation.

**Financial support and acknowledgements:** CNPq/Brazil (grant), CAPES/Brazil (scholarship) and PPGCF/UFRGS.

**Ethical approval:** CEUA/UFRGS Ethical Committee, number 30012.
BICONTINUOUS MICROEMULSION CONTAINING FLAVONE: A PHYSICOCHEMICAL AND MORPHOLOGICAL CHARACTERIZATION

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Bicontinuous microemulsions (BME) occur when the aqueous and oil phases are at similar amount and present a surfactant concentration to reduce the interfacial tension between the phases. The flavone (FL), a flavonoid compound is lipophilic molecule and show antimicrobial and anti-inflammatory activity. Because of this, FL is a potential molecule to be incorporate in BME systems. The aim of this work was develop and characterize a FL-BME for topical application. The system was produced with the construction of the pseudoternary phase diagram, using Kolliphor® HS15/Span® 80 (9:1), as surfactants, isopropyl myristate, as oil phase, and deionized water, as aqueous phase. A formulation was selected and FL incorporated at the concentration of 1 mg/ml. This system was characterized by macroscopic appearance, pH, differential scanning calorimeter (DSC) e transmission electron microscopy (TEM). The system presented as semi-solid, transparent, and homogeneous after 48h. The analyzes were performed with the blank BME (BK-BME) and FL-BME, and the pH for cutaneous administration were 7.17 and 7.15 respectively. For the formulations, the DSC present two exothermic peaks (MEB-BK - 16.56°C; -33.81°C; MEB-FL -16.60°C; -30.10°C) , one attributed to the peak of freezing of water and another related to oil, maining that the systems is realy bicontinuous. The TEM showed a linear structure, suggesting stripe agglomerates for BK-BME and FL-BME. So, the developed system was presented as a BME and with acceptability for cutaneous administration, presenting itself as an alternative for the topical anti-inflammatory and antimicrobial treatment.

DEVELOPMENT, CHARACTERIZATION AND LIBERATION PROFILE EVALUATION OF LIPID-CORE NANOCAPSULES AND NANOEMULSION CONTAINING A MODEL ACTIVE SUBSTANCE

MANUELA DE CASTILHOS FRANÇA GONÇALVES, KELLY CRISTINE ZATTA, ADRIANA RAFFIN POHLMANN, SÍLVIA STANIÇUASKI GUTERRES

Lipid-core nanocapsules (LNC) have been shown to be promising tools for several active substances incorporation in cutaneous treatment. Factors such as polymer molecular weight and nanocarrier system may influence the profile of different active substances release. The purpose of this study was to develop and characterize the LNCs prepared with different molecular weight polymer, or in its absence (nanoemulsion - NE), and to evaluate the profile of a model active substance release from these nanoparticles. Materials and methods: The formulations were prepared by the interfacial deposition of the preformed polymer method using poly (ε-caprolactone) (PCL) with different molecular weights (MW = 14.000 g / mol, MW = 80.000 g / mol), LNC14 and LNC80, respectively, or in polymer absence, NE and characterized in terms of pH, encapsulation efficiency, diameter and polydispersity by laser diffraction and dynamic light scattering. The release studies were performed using a dialysis bag and all experiments were conducted under sink condition. Results, discussion and conclusion: LNCs and NE suspensions presented pH values between 5.63 and 5.84, encapsulation efficiency of LNC80 particles 54.4% (LNC80), 37.08% (LNC14) and 31.72 % (NE) and mean particle size around 200 nm, suitable for topical application. The low polydispersity indexes ranged between 0.114 and 0.165, showing a homogeneous distribution and the zeta potential values were negative between -8.55 to -17.10, characteristic of stable colloidal suspensions. In general, the three nanoparticle suspensions showed similar release profiles. It was observed a slower initial release from LNC80 compared to LNC14 and NE, probably due to a higher nanoencapsulated active substance concentration and a large rigidity of this nanoparticle wall.

Financial support and acknowledgement: CAPES, CNPq, PPGCF/ UFRGS.
EVALUATION OF THE INFLUENCE OF THE TENSIOACTIVES IN THE PREPARATION OF POLYMERIC NANOCAPSULES CONTAINING ESSENTIAL OIL OF Psidium cattleianum Sabine

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Introduction: in the preparation of nanocapsules, the surfactants are responsible for the formation and stability of these nanostructures, impeding or retarding the phenomena of aggregation, sedimentation or loss of the nanoencapsulated active substance. The essential oil of Araçá red (Psidium cattleianum Sabine) has antifungal properties, however this oil is highly unstable and nanoencapsulation is an alternative to stabilize this oil. Objectives: To verify the influence that the amount and type of surfactants exerts in the preparation and in the physical-chemical characteristics of the NCs containing the araçá oil. Materials and methods: Poly(ε-caprolactone) nanocapsules were prepared by the nanoprecipitation method, with a final concentration of essential oil of 5mg / mL. Different amounts and types of surfactants were used: NC1-SP80/TW80 (0.077g /0.077g), NC2-SP60 / TW80 (0.077g / 0.077g), NC3-SP80 / TW80 (0.0385g / 0.077 g), NC4-SP80 / TW80 (0.077g / 0.154g), NC5-SP60 / TW80 (0.154g /0.077g) and NC6-SP60/TW80 (0.154g/0.154g). The characterization tests were: macroscopic evaluation, mean particle diameter and Zeta potential. Results: NC1, NC2, NC5 and NC6 presented Zeta values of -3.75; -18.5, -26.7; -30, PDI 0.275; 0.173, 2.14; 1.33 and mean particle diameter of 281.7nm; 221.5nm, 249.4nm; 224nm, respectively. NC3 and NC4 were excluded by the formation of lumps. Conclusion: NC5 and NC6, presented more negative zeta in module, being more suitable. The PDI of NC1 and NC2 was compatible with a monodisperse system. Formulations prepared with Span 60 and lower amounts of Tween showed more adequate results, however stability tests should be conducted. Acknowledgment: PRONEX FAPERGS/CNPq 12/2014 número 16/2551-0000467-6.

COMPARATIVE STUDY OF LIPID-CORE NANOCAPSULES (LNC) AND NANOEMULSION BEHAVIOR IN CUTANEOUS PENETRATION-PERMEATION

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Introduction: Dermatological application of nanoparticles associated drugs represents a promising strategy to reduce irritation and allergenicity and increase the treatment efficacy, in which lipid-core nanocapsules (LNC) have shown great potential and applicability. However, it is still unknown the influence of polymer molecular weight or its absence (nanoemulsion) in the active substance cutaneous penetration-permeation and release. In this work, we evaluated the cutaneous distribution from three different carrier systems. Methods: Three nanosystems were produced using a model active substance with partial encapsulation efficiency (EE%): a) LNC14 – prepared with poly(ε-caprolactone) (PCL) Mw 14.000 g.mol-1, b) LNC80 - prepared with PCL Mw 80.000 g.mol-1, c) NE – prepared without polymer. The formulations were characterized by mean particle size (dynamic light scattering), zeta potential (electrophoretic mobility), pH, and active content. The permeation-penetration study (24h) were performed in vitro in Franz diffusion cell, using porcine ear skin as a limiting barrier. Results: The LNC80 particles (54.4% EE), LNC14 (37.08% EE) e NE (31.72% EE) showed mean diameter between 170 e 200 nm, negative zeta potential, and 500 mg/mL active content. The total amount of permeate was similar (p>0.05) between LNC14 (23.6±0.62 µg/cm²) and NE (26.2±7.34 µg/cm²), which were significantly higher than LNC80 (15.6±1.97 µg/cm²) (pµg/cm²/h, 0.65±0.20 µg/cm²/h, and 0.41±0.04 µg/cm²/h, to LNC14, NE and LNC80, respectively. The amount of active substance retained in the stratum corneum, epidermis and dermis for LNC80 (3.30±0.05 µg/cm², 3.10±0.58 µg/cm², 14.82±2.92 µg/cm², respectively), was higher than LNC14 (1.28±0.38 µg/cm², 2.28±0.34 µg/cm², 10.43±1.10 µg/cm², respectively), and NE (1.17±0.09 µg/cm², 2.01±0.51 µg/cm², 9.17±0.44 µg/cm², respectively) (p>0.05). Discussion and conclusions: The three nanosystems were able to penetrate through different skin layers, reaching the medium receptor. The high molecular weight polymer nanocapsule (LNC80) allowed a higher EE% substance active, which may have contributed to a lower cutaneous permeation, getting retained in skin layers, mainly in dermis. Financial support and acknowledgement: CAPES, CNPq, PPGCF/ UFRGS.
INFLUENCE OF COSMETIC PREPARATIONS WITH DIFFERENT SULFATE CONCENTRATIONS ON HAIR PROTEIN LOSS

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There is a great variety of dermocosmetics hair products in the market, where the consumer’s choice is defined by advertising. Recently, the presence of sulfate in these formulations (as a surfactant) has been the subject of questioning the possibility of hair protein loss caused by the continuous use (BONILHA, CANTO, 2013). This led to the popularity of “low poo” preparations, with low sulfate concentration, and “no poo” preparations, without the presence of sulfate (MASSEY, 2001). Due to the small number of scientific findings, this work aimed to investigate the correlation between sulfate concentration and hair protein loss. Commercial preparations were then selected and classified according to the sulfate concentration in: traditional shampoos; “low poo”; and “no poo”, totaling 6 products (n = 2). Sample of virgin hair was divided into hair locks (0.5g), which were individually submitted to 30 cycles of standard washings using each of the products selected for further assessment of sulfate dosing by spectrophotometry (TABATABAI, 1974), and protein loss in hair by the Lowry method (1951). As main results, quantification of sulfate ratified label information and the “no poo” preparations did not show significant protein loss. However, traditional shampoos caused less hair protein loss than low poo preparations, suggesting no correlation between sulfate concentration and hair protein loss. However, because these are complex formulations, there may be interference from the other constituents. Thus, as a perspective for further studies, solutions containing only sulfate in different concentrations will be formulated to make more conclusive statements.

IMMUNOGENICITY OF A MALARIA VACCINE CANDIDATE BASED ON ALLELIC FORMS OF THE PLASMODIUM VIVAX CIRCUMSPOROZOITE PROTEIN ADMINISTERED IN MICE USING DIFFERENT ADJUVANT FORMULATIONS

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Introduction: The development of an efficacious vaccine against Plasmodium vivax would contribute greatly to control malaria transmission. Recently, we developed a hybrid polypeptide based on P. vivax Circumsporozoite protein named PvCSP-All epitopes. This hybrid contains the conserved C termini of PvCSP and the three variant repeat domains in tandem, which was able to elicit strong antibody mediated immune responses in mice to each of the three allelic forms of this antigen (VK210, VK247 and P. vivax-like). The present study aims to evaluate the immunogenicity of the PvCSP-All epitopes in the presence of adjuvants applicable for human use. Methods: The protein PvCSP-All epitopes was expressed in Pichia pastoris yeast. C57BL/6 mice were immunized subcutaneously with three doses of the antigen (10 µg) in the presence of adjuvants Polyrribinosinic:polyribocytidyl ylic acid (Poly I:C, Invivogen), Montanide® ISA 720 (Seppic) and squalene-based adjuvants [AddaVax™ and IB160 (Butantan Institute)]. The IgG antibodies against the three P. vivax CS proteins were determined by ELISA in sera from mice two weeks after each immunizing dose. This study was approved by the Ethical Committee of the School of Pharmaceutical Sciences (USP) under the no 74.2016-P531. Results and discussion: Mice immunized with PvCSP-All epitopes generated high IgG titers specific to all CSP alleles. Our results demonstrated that it is possible to elicit a strong humoral response to PvCSP alleles in mice in the presence of different adjuvants, including a TLR-3 agonist. Conclusion: Therefore, these promising formulations will be selected for trials in non-human primates under GLP condition. Financing: FAPESP 2012/13032-5 and 2014/18102-7, CNPq-INCTV, CAPES.
**EVALUATION OF DSPE-PEG INSERTION IN LIPOSOMES**

IARA MAIRA DE OLIVEIRA VIANA, NICOLAS BERTRAND, ELIANA MARTINS LIMA

**Introduction:** Multiple commercialized liposomal formulation are prepared with N-(carbonyl-methoxypolyethylene glycol)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE-PEG). Due to steric stabilization, PEG coverage confer long circulation times to liposomes. PEGylated liposomes can be prepared by inserting PEGylated lipids before or after formation of unilamellar vesicles, techniques respectively coined the pre- or post-insertion method. The post-insertion of PEGylated lipids might lead to high coverage of the outer layer of the liposomes, improving steric effect. The purpose of this work is to evaluate the coverage of PEG in liposomes prepared by pre- and post-insertion techniques. **Methods:** Phosphatidylcholine (PC), cholesterol (CHOL) and DSPE-PEG were used to prepare liposomes. All lipids were dissolved in chloroform followed by evaporation in rotavaporator. The thin lipid film was hydrated with isotonic buffer. The vesicles were extruded through polycarbonate membrane. In order to prepare PEGylated liposomes by post insertion technique, nonPEGylated liposomes of PC and CHOL were prepared. A film containing DSPE-PEG were hydrated with nonPEGylated liposomes. The free DSPE-PEG were separated by size-exclusion chromatography. The amount of DSPE-PEG were determined by high performance liquid chromatography (HPLC). The total phospholipids were quantified by colorimetric assay. **Results:** Liposomes with diameters of approximately 100 nm were synthesized. HPLC method showed to be suitable for the determination of DSPE-PEG from liposomes. Size-exclusion chromatography allowed the separation of free DSPE-PEG from PEGylated liposomes. The insertion of DSPE-PEG on liposomes membranes appear to be dependent on temperature and incubation time. **Conclusion:** PEGylated liposomes with high PEG coverage may be prepare successfully by post insertion technique.

**Acknowledgements:** This work was supported by CAPES, CNPQ, FUNAPE and FINEP.

**HOST-GUEST INTERACTION OF THYMOL WITH β-AND HYDROXYPROPYL-β-CYCLODEXTRIN: PREPARATION AND PHYSICOCHEMICAL CHARACTERIZATION**

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**Introduction:** Thymol (TM) is a phenolic compound with several pharmacological activities elucidated in the literature such as anti-inflammatory, antitumor and antimicrobial. This study aimed to prepare and characterize inclusion complexes of TM/β-CD and TM/HPβ-CD. **Methods:** The samples were prepared with βCD and HPβ-CD by freeze-drying (FD) method in molar ratios of 1:1. Molecular docking, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), Karl Fischer titration (KFT), thermogravimetric analysis (TG/DTG), Fourier-transform infrared spectroscopy (FTIR) and entrapment efficiency (EE%) by high performance liquid chromatography (HPLC) were used for the characterization of the complexes. **Results and discussion:** The docking showed possible formation of inclusion complexes with favorable energy (-3.45 kcal.mol$^{-1}$) for both CDs. The SEM images showed that reduction in the crystal structure of TM exhibited smaller crystals with different morphology for TM/βCD and TM/HPβ-CD. Corresponding DSC curves TM/β-CD and TM/HPβ-CD did not show any endothermic peak in the temperature range of thymol volatilization, indicating the inclusion of thymol inside cavity complexes and TG/DTG curves showed mass loss both for TM/β-CD as for TM/HPβ-CD with 8.89% and 5.61%, respectively (115-325°C). FTIR analysis evidences a strength interaction among thymol and each of the CDs (β-CD and HPβ-CD), the spectrum showed variations in intensity and bands between 944 cm$^{-1}$ and 807 cm$^{-1}$. The EE% obtained was 65% for β-CD and 60% for HPβ-CD. **Conclusions:** The results showed that thymol formed inclusion complexes with both CDs, mainly with TM/β-CD. This study can contribute to other studies involving this type of system.
IN VITRO RELEASE KINETICS OF MINOXIDIL SULFATE MICROEMULSIONS WITH Cucurbita pepo OIL

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Introduction: Minoxidil is a drug known to stimulate growth, and the treatment of androgenic alopecia. The aim was to evaluate the release of Minoxidil Sulfate (MNS) in microemulsions (ME).

Methods: In vitro release kinetics were performed on 6 Franz diffusion cells, diffusional area of 1.77 cm², volume ± 15 ml, cellulose nitrate artificial membranes, pH 7.4 phosphate buffer solution, thermostated bath with circulation at 32 ± 0.5 °C at 100 rpm for 6 hours. The MNS quantification was by UV spectroscopy at 286 nm. Statistical analysis by ANOVA One-way followed by Tukey post-test.

Results and discussion: Two 3% microemulsions of MNS (ME1 MNS3% and ME2 MNS3%), two of 5% (ME1 MNS5% and ME2 MNS5%) and two hydroalcoholic formulations (C3% and C5%) were obtained. C5% Formulation released a larger amount of MNS, presenting a significant difference with 3% ME (5,892.82, 2,239.95 and 2,495.65 μg/cm², respectively). The controls adapted to the Higuchi model and the ME to the first order and zero order model. The presence of ethanol in the controls may have accelerated the release of MNS. The MEs released in a more controlled way.

Conclusions: Formulations of 5% ME did not show significant differences in relation to hydroalcoholic formulations. The formulations released more than 59% of MNS, thus presenting promising characteristics for in vitro permeation tests. The microemulsion did not imprison the drug and may be an alternative to products with alcohol.

ANALYTICAL METHOD VALIDATION BY UV SPECTROSCOPY FOR QUANTIFICATION OF MINOXIDIL SULFATE IN MICROEMULSIONS

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Introduction: Alopecia is not only a medical condition, but often involves devastating social aspects in the patients. More than 30-40% of the male population over the age of 20 show androgenic alopecia or male pattern hair loss. The aim is the validation of an analytical method for quantification of Minoxidil Sulfate (MNS) in microemulsions.

Methods: The analytical method was validated by the analysis of the parameters of specificity, linearity, limit of detection (LoD), limit of quantification (LoQ), precision, accuracy and robustness according to Resolution 166/2017 of the ANVISA and guide Analytical Procedures and Methods Validation for Drugs and Biologics of the U.S. Department of Health and Human Services (FDA).

Results and discussion: The wavelength selected was the highest absorption (286 nm). The equation of the line was y = 0.0555-0.0623, where the highest CV% was 2.06, r² = 0.997, the curve was linear, LoD = 0.47μg, LoQ = 0.71μg, the method was required, where the repeatability had DPR% = 0.024%, and the intermediate accuracy did not present a significant difference for p.

Conclusions: The method was linear, specific, accurate and robust for the parameters evaluated in the current legislation and can help in the dosing of new systems with minoxidil.
FABRICATION OF COMPOSITE SCAFFOLDS INCORPORATING NATURAL NANOMATERIALS FOR BONE TISSUE ENGINEERING

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There is considerable interest in the pharmaceutical and biomedical areas for the development of composite scaffolds produced with biopolymers, as matrices for bone tissue engineering. For this reason, we attempted to fabricate composite scaffolds by the combined method involving the incorporation of nanomaterials in different polymeric matrices (alginate and gelatin). The formed hydrogels was poured into plastic molds and freeze-dried to form composite scaffolds to be applied to the bone tissue. The prepared scaffolds were evaluated by differential scanning calorimetry (DSC), thermogravimetric analysis (TG/DTG), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), hydration capacity and mechanical properties. The cytotoxicity of the prepared composite scaffolds was performed by alamar blue assay on J774 cell line. The characterization results revealed that composite scaffolds exhibited good 3D architecture with well-defined porous structure, improved compressive strength and regulated biodegradation. In addition, the incorporation of alginate at concentration of 1% provided elegant and flexible scaffolds (higher Young’s modulus) and gelatin scaffolds showed higher stability at physiological pH and excellent swelling behaviors. FTIR results provided evidence of intermolecular interactions between alginate and nanomaterial, and the presence of a cross-linked nanomaterial network in the alginate matrix. SEM images demonstrated that alginate scaffolds has the largest average pore diameter in comparison to gelatin materials with irregular and smaller pores. The cell viability results indicated that the designed scaffolds had no significant cytotoxicity. Therefore, these interesting properties open the way for the application of this biomaterial for bone tissue engineering.

Acknowledgments: CAPES, CNPq, ITP/UNIT and FAPITEC/SE for the financial support and fellowships.

DEVELOPMENT AND PHYSICAL-CHEMICAL CHARACTERIZATION OF AVOBENZONE LIPID-CORE NANOCAPSULES

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Introduction: Avobenzone (AVO) is a UVA filter commonly used in photoprotective formulations. However, its photostability and incompatibility with other sunscreens has been constantly discussed. The nanotechnology based formulations probably allow an increase in this filter stability and consequently an increase in its skin effectiveness. The present work, therefore, aimed to develop and characterize physicochemically the nanoformulations containing avobenzene at concentrations of 1.0 mg / mL and 2.5 mg / mL. Methods: LNC-AVO-1.0mg / mL and LNC-AVO-2.5mg / mL were prepared by the interfacial deposition of the preformed polymer method. Subsequently, they were characterized in terms of size distribution profile by laser diffraction and dynamic light scattering techniques, as well as the electrophoretic mobility, pH and AVO content by high performance liquid chromatography (HPLC). Sample preparation and analysis procedure was performed in triplicate.

Results and discussion: LNC-AVO-1.0mg / mL nanoformulation showed a mean particle size distribution of 229.3 ± 3.6 nm with monodisperse population, negative zeta potential (-14.23 ± 1.67 mV) and pH 5.84 ± 0.08. LNC-AVO-2.5mg / mL formulation exhibited a mean particle size distribution of 199.46 ± 1.8 nm, with negative zeta potential (-11.3 ± 1.65 mV) and slightly acid pH 5.91 ± 0.91. The determination of suspension AVO contents were around 99%. The zeta potential and pH values corroborate with literature studies for topic application formulations.

Conclusion and perspectives: Results demonstrated that AVO nanoformulations have potential for future studies related to photostability and photoprotection and still may be linked to antioxidants substances.

Financial support and acknowledgement: CAPES, CNPq, PPGCF/ UFRGS.
FUNCTIONALIZED PLGA NANOPARTICLES IMPROVES THE BENZNIDAZOLE EFFICACY AS ANTICHAGASIC AND CHEMOTHERAPEUTIC AGENT

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Introduction: Several polymers have been investigated for producing nanocarriers due to their ability to cross biological barriers. PLGA (Poly (D, L-lactide-co-glycolide) is a copolymer highlighted due to their biocompatibility and low toxicity. The purpose of this study was to produce functionalized biodegradables nanoparticles with sialic acid and cholesterol able to overcome cell membranes and improve the biological activity of benznidazole (BNZ) in cancer cells and Chaga’s diseases. Methods: The performance of the selected formulations and procedure parameters were monitored using a wide experimental approach including particle size, polydispersity index, zeta potential, atomic force microscopy (AFM), scanning electron microscopy (SEM), attenuated total reflectance Fourier transforms infrared spectroscopy (ATR– FTIR), encapsulation efficiency and in vitro assays. Results and discussion: Spherical and stable sub 300 nm polymeric nanoparticles were optimized, with the encapsulation efficiency greater than 95%. The in vitro drug release kinetics demonstrated a slow release adjusted by mathematical models, which depended on the drug / copolymer ratio used. In addition, the cell viability assays using the normal kidney cells (HEK 293), human colorectal cancer cells (HT-29) and cardiac myoblastic cells (H9c2) demonstrated the biocompatible of the nanoparticles and the improvement the biological activity of BNZ. Assays made with cells infected with with epimastigotes (Y, CL-Brenner and Dm28c strains) and amastigotes (H9c2 and Dm28c strains) show an increase in the potency of the nanoparticles over free BNZ. Conclusions: The results demonstrate success in performance assays and this novel BNZ-loaded polymeric nanoparticles has great potential as antichagasic and chemotherapeutic.

DEVELOPMENT OF NANOCARRIERS FOR COMBINED DELIVERY OF CISPLATIN AND DEXAMETHASONE FOR THE TREATMENT OF GLIOBLASTOMA MULTIFORME

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Introduction: Glioblastoma multiforme is one of the cancer types with the worst prognoses; even with surgical removal, radiotherapy and chemotherapy, patients have a low life expectancy. Temozolomide and cisplatin are the most frequently used chemotherapeutics for its treatment, but their multiple side effects limit their use. In addition, synthetic glucocorticoids, such as dexamethasone, are used as adjunctive treatment to reduce edema, but they also have several side effects. Thus, it is imperative to find new strategies to optimize glioblastoma treatment. This work aims to develop a nanocarrier for co-encapsulation of cisplatin and dexamethasone to improve cell cytotoxicity while reducing individual drug concentrations necessity for the effect to minimize adverse effects and improve treatment. Methods: We developed phosphatidylcholine-based nanoemulsions containing poloxamer 188 to aid passage through the blood-brain barrier, and the influence of poloxamer concentration (0-1% w/w) on size, zeta potential and stability (at room temperature) was assessed. Results and discussion: All formulations displayed size below 200 nm, polydispersity index (PDI) below 0.250 and negative zeta potential (-3 to -8 mV). Formulations containing poloxamer at any concentration showed PDI increased about 2-fold during storage for 30 days at room temperature, even though the average size did not change in a pronounced manner; this effect was more perceptible with poloxamer at 1%, thus, we suppose that in higher concentrations the poloxamer in the formulations can form micelles and increase the PDI. Conclusions: Our results demonstrate the feasibility of obtaining nanoemulsions containing poloxamer 188 to aid drug transport across the blood brain barrier.
EVALUATION OF IN VITRO RELEASE KINETICS OF RIPARIN C IN TRANSDERMAL NANOCARRIER

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Introduction: Alkaloids were isolated from the green fruit of Aniba riparia (Nees) Mez (Lauraceae), the riparins I, II and III. Structural analogues of such molecules (riparins A-F) have been experimentally obtained and have been presenting several pharmacological activities. The objective this work is evaluation of in vitro release kinetics of riparin C in transdermal nanocarrier.

Methods: The study was conducted using dialysis membranes in Franz type diffusion cells (1.77 cm²). The nanocapsules were produced by interfacial deposition of preformed polymer method and characterized by transmission electron microscopy. The formulations presented a quantity released Q6h (µg/cm²·h±SD): 20.99±6.34, 24.88±8.13 and 34.08±3.57. As for the kinetic model, ME1 and control behaved as a first order model, with the highest r² values of 0.9679 and 0.9891, respectively. ME2 showed kinetic behavior of Higuchi (0.9677).

Conclusions: The formulations ME1 and ME2 presented good release profile in vitro and were promising for their use as nanocarriers for use by the route of administration transdermal.

DEVELOPMENT AND CHARACTERIZATION OF POLYMERIC NANOCAPSULES CONTAINING NEROLIDOL FOR THE TREATMENT OF EXPERIMENTAL ARTHRITIS

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Introduction: Nerolidol has wide biological activities including anti-inflammatory. However, has high volatility and low solubility. In this context, nanotechnology may be used as alternative to improve stability of this compound. The objective of study was to develop and characterize polymeric nanocapsules containing nerolidol and evaluate its activity on zymosan-induced arthritis model.

Methods: The nanocapsules were produced by interfacial deposition of preformed polymer method and characterized by particle size, pH, polydispersity index (PDI), zeta potential, encapsulation efficiency (EE%) and transmission electron microscopy (TEM). In vitro citotoxicity of formulations was evaluated by alamar blue and MTT assays in J774 cells for 72 hours. In vivo neutrophils migration assay was performed on intra-articular zymozan-induced arthritis model in mice (CEPA/UFS #22/2018 protocol number).

Results and discussion: Nerolidol-loaded nanocapsule suspensions presented adequate properties: mean diameter of particles of 223.8 ± 6.6 nm, pH values of 6.84 ± 0.1, PDI ≤ 0.2, zeta potential -21.7 ± 3.7 mV and EE of 80.2 ± 1.3%. TEM images confirmed the nanometric dimension and showed spherical particles. The formulations studied did not demonstrate cytotoxicity under conditions evaluated. Nerolidol (300 mg/kg) inhibited neutrophils migration into joint cavity by 64.7% (IC₅₀ = 2.5 mg/kg) compared with the control group and nerolidol-loaded nanocapsules (3 mg/kg) inhibited in percentage similar to free nerolidol (10 mg/kg).

Conclusions: The data suggests that nanoencapsulation of nerolidol improved its physicochemical properties and anti-inflammatory effect on arthritis in mice. Subsequently, in vitro release and permeation studies and in vivo pharmacokinetic studies will be performed.

Acknowledgments: CAPES, CNPq, FINEP and FAPITEC/SE for the financial support and fellowships.
OPTIMIZATION BY BOX-BEHNKEN DESIGN OF A NANOSTRUCTURED LIPID CARRIER FOR TOPICAL DELIVERY OF CLOBETASOL PROPIONATE

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Introduction: Lipid nanoparticles emerged in the early 1990s as a promising alternative to traditional colloidal systems because of their excellent physicochemical stability. The aim of this present study was to develop and optimize a nanostructured lipid carrier (NLC) for clobetasol delivery. Methods: To obtain the NLC, the oil phase together with the surfactants and the aqueous phase were separately heated up to 75 ± 5°C. Then, the aqueous phase was poured into the oil phase and then sonicated. The influence of surfactant composition (Tween 20/Span 80 ratio) were evaluated for 30 days. Results and discussion: It was observed that at 1:1 composition, the lowest particle growth rate (3.86%) and a final size of (132.23 ± 15.24) nm were achieved after 30 days. Box–Behnken experimental design was applied for optimization of solid lipid nanoparticles. Input variables were time and power used for sonication, amount of surfactants, of lipid phase, of liquid lipid in lipid phase and clobetasol. Particle size and polydispersity index (PDI) were considered as a response. It was observed that, lowering the amount of lipid phase (2%) and increasing the liquid lipid composition in the lipid phase (48%), the particles exhibited the smallest sizes (~ 160 nm). For narrow PDI, it was necessary to increase the amount of surfactants (7.8%) (PDI ~ 0.2). Moreover, it was necessary to increase the time (9 min) and power of sonication (40%). Conclusion: As all variables were significant, further analysis must be done to observe the long term stability of NLC.

LAYERED DOUBLE HYDROXIDES AS PROMOTERS OF SUSTAINED RELEASE OF DRUGS: A BIBLIOGRAPHIC SURVEY

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The relentless search for new carrier materials that are biocompatible and that show low toxicity, has guided the development of new pharmaceutical formulations that incorporate these substances in their compositions. Layered double hydroxides (LDH) are inorganic solids used in pharmaceutical and chemical sciences as catalysts, polymers and stabilizers of drugs, adsorbent agents and modulators of the release of active substances. With the aim of knowing and making a theoretical foundation about LDHs as promoters of sustained release of drugs, a bibliographical survey was performed using the databases Scielo, Pubmed and Science Direct, covering articles published between 2008 and 2018, in Portuguese and English. Since LDHs are alkaline compounds, they dissolve rapidly at low pH values, but their dissolution is reduced considerably at higher pH values, allowing the slow release of the drugs. They have the ability to intercalate biologically active substances in their interlamellar region, or to adsorb these substances on their vast surface area. These properties allow LDH to be one of the inorganic materials indicated as promising in the storage and in the modified release of the intercalated substance, and it may be associated with drugs with low plasma half-life or in chronic therapies, so they remain in the bloodstream at an effective dosage over a longer period of time. This strategy allows the reduction of the side effects and the increase of the patient adhesion to the treatment.
INFLUENCE OF CRITICAL FORMULATION PARAMETERS ON THE TECHNOLOGICAL AND BIOPHARMACEUTICAL PROPERTIES OF FELODIPINE-LOADED LIQUISOLID PELLETS MANUFACTURED BY EXTRUSION-SPHERONIZATION

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Introduction: Liquisolid systems are used to enhance drug dissolution rate and extent, improving oral bioavailability of poorly-soluble drugs. However, loading high amounts of non-volatile solvents (NVS) in liquisolid systems can be challenging. In this study, felodipine-loaded liquisolid pellets were obtained by extrusion-spheronization to assess the manufacturing feasibility and potential improvements in drug dissolution kinetics. Methodology: Felodipine (5, 10, 20% w/w), NVS Kolliphor® EL (0, 30, 40% w/w) and crospovidone loads (10, 30, 40% w/w) were the critical formulation parameters assessed. Using a factorial design, the impact of these parameters on technological and biopharmaceutical responses was assessed, such as the solubility of the liquid medication in the dissolution medium (ANOVA, \( p < 0.05 \)). Results and discussion: All formulations were feasible by a manufacturing perspective. Batch yield was at least 62.92%, with medium diameters averaging between 0.38 – 1.20 mm. Carr’s indexes and angle of repose values were found between 0.5 – 10.83% and 25.3 – 28.95º respectively. Yield, granulometric distribution and angle of repose increased as the drug and NVS loads increased. Increased drug dissolution rate and extent were found reducing felodipine and increasing NVS loads. NVS was also correlated with an increase in solubility of the liquid medication in the dissolution medium. Conclusion: Liquisolid pellets are still a recent advance in the multiparticulate field and a better understanding of the impact of critical formulation parameters on product feasibility and performance is needed. Herein, it has been demonstrated the successful manufacturing of liquisolid pellets with high NVS load and adequate technological and biopharmaceutical properties.

Funding source: CAPES

CHARACTERIZATION OF LIPID-CORE NANOCAPSULES CONTAINING LEVOTHYROXINE AND ITS PROTECTION AGAINST EXPOSURE TO UVA LIGHT

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Introduction: Levothyroxine is the choice drug for hypothyroidism treatment. However, this drug therapy presents some difficulties, due to the fasting necessity, as well as its instability against environmental factors. An strategy that may be employed to overcome these problems is the drug nanoencapsulation. Objective: This aimed to develop and characterize lipid-core nanocapsules (LNC’s) containing levothyroxine, as well as the evaluation of photostability against UVA light. Methodology: Levothyroxine LNC’s (10 \( \mu g/mL \)) were developed, in duplicate, employing the interfacial deposition of preformed polymer method and subsequently characterized in terms of particle size and polydispersity index. The photostability evaluation was performed through the UVA light particles exposure, in a mirror chamber. The levothyroxine content was analyzed by HPLC-UV at pre-established times. The reaction order was determined and the degradation constant and ½ life-time were calculated. Results and discussion: The nanocapsules containing levothyroxine presented a homogeneous size distribution with particle size of 151.85 ± 2.33 nm and the polydispersion index of 0.06 ± 0.01. The photodegradation study showed a drug protection from the nanocapsule, since the ½ life-time of nanoencapsulated drug was over 60 hours, whereas the free drug time was less than 10 hours. Conclusions: Lipid-core nanocapsules containing levothyroxine showed appropriate physico-chemical characteristics and proved to be a strategy to protect the drug against UVA light.
CHARACTERIZATION OF AZITHROMYCIN-LOADED MICROEMULSIONS FOR TOPICAL USE

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Azithromycin (AZ) is a promising macrolide antibiotic for the treatment of bacterial skin infections due to their capacity of penetration in the tissues and wide spectrum of action for several bacterial species. It presents an elevated partition coefficient (log P = 3.04), which enables it to be incorporated into O/W microemulsions (ME). The aim of this work was to characterize an AZME. The formulation studied was composed of deionized water, isopropyl myristate, LAS® and Brij® 52 (9: 1) and AZ (20 mg/ml). This system was characterized by polarized light microscopy (PLM), dynamic light scattering (DLS), polydispersity index (PDI), transmission electron microscopy (TEM) and differential scanning calorimetry (DSC). The visualization of dark fields by the technique of PLM confirmed the isotropic character of the ME. TEM indicated the nanometric droplet size of the systems and the DLS technique (n = 10) measured a diameter of 18.72 ± 0.63 and 20.89 ± 0.24 nm for AZ-free ME and AZME, respectively. PDI values obtained were 0.172 ± 0.005 (AZ-free ME) and 0.166 ± 0.008 (AZME), both with monomodal dispersion. Thermograms obtained by DSC evidenced the behavior of ME resembled the thermal events of the water thermogram, indicating an O/W type system. Therefore, this characterization evidenced an optimal AZME for its application to the skin and may represent a new effective alternative in the treatment of cutaneous infections.

Funding agencies: CAPES, UEPB-PROPESQ.

PREPARATION AND CHARACTERIZATION OF CURCUMIN NANOCAPSULES COATED WITH CHITOSAN FOR ORAL SQUAMOUS CELL CARCINOMA TREATMENT

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Introduction: Oral squamous cell carcinoma is a malignant neoplasm that originates in the epithelium and represents the most prevalent malignant tumor of the oral cavity. Considering the high incidence of side effects of classic antineoplastic drugs, the search for new therapeutic is a relevant topic for news antineoplastic pharmacotherapeutics. Our objective was to develop and characterize curcumin-loaded chitosan-coated nanocapsules in order to improve mucoadhesion, consequently improving permeation through the oral mucosa after topical administration. Methods: The formulation was prepared using the interfacial deposition of polycaprolactone (PCL) and coated with chitosan, the curcumin final concentration was 0.9 mg.mL⁻¹. The granulometric profile was determined by laser diffraction technique: the z-average by photon correlation spectroscopy, zeta potential of the formulations by electrophoretic mobility and the pH by potentiometry. The curcumin content of the formulation was determined by HPLC (previously validated method) and the encapsulation efficiency by ultrafiltration-centrifugation. Results and discussion: The aspect of the formulation was described as a milky suspension. Curcumin formulation presented homogeneous diameter distribution with span values around 1.5. The D₄₃ after coating was 179±48 nm and z-average 200±20 nm. Confirming the presence of chitosan at the interface of the nanocapsules the zeta potential was +19.00±3.18 mV and the pH was 4.03. The curcumin content in the formulation was 99.29±3.61 % and the encapsulation efficiency very close to 100%. Conclusion: The characterization of the nanocapsules ensured that the formulation is satisfactory from a technological point of view and promising for future studies.

Financial support and acknowledgement: CAPES, CNPq, PPGCF/ UFRGS, FAPERGS 17/2551-0000
COMPARATIVE EVALUATION OF THE ANTIBACTERIAL AND ANTIOXIDANT ACTIVITIES OF THE ESSENTIAL OIL OF ROSMARINUS OFFICINALIS L OBTAINED BY CULTIVARS ORGANICALLY AND CONVENTIONALLY

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Introduction: Essential oils have promising potentials for maintaining and promoting health, as well as preventing and potentially treating some diseases. Rosmarinus officinalis L. essential oil (ROES) has been attributed antioxidant, anti-inflammatory, antimicrobial, fungicidal, and anticancer activity. The aim of the present work was to study in vitro anti-oxidant (AntiOx) and antibacterial (AntiBac) activities of the samples of ROES from organically and conventionally grown cultivars. Methods: One sample was obtained commercially from the Ferquima company (A1) and two organics samples were obtained from France (A2) and Brazil (A3). The antibacterial activities were determine by disc diffusion assay against Staphylococcus aureus: ATCC 25923 and strains of bovine mastitis (5418 e 5420) and AntiOx activities were studied using several free radical scavenging assays such as the TROLOX equivalent antioxidant capacity (TEAC). Results and discussion: We observed AntiOx and AntiBac activities for all samples analyzed. Sample A1 presented a bacteriostatic effect in ATCC strain and a small inhibition halo in strains 5418 and 5420 (8.3±0.3; 9.1±0.3 mm). Sample A2 also had a bacteriostatic effect in S. aureus ATCC 25923 and large inhibition halos that could not be measured for the other strains. To sample A3 was not able to measure the halos, showing inhibition far superior to that observed in relation to the other oils. The TEAC values of 14.56 ± 0.67; 1.1249 ± 0.08 and 54.03 ± 1.08 mM/kg respectively. Conclusions: These preliminary studies showed promising results since ROES from Brazil cultivars organically may provide an alternative to promote its use as a natural medicines.

PHOTOTOXICITY EVALUATION OF CAFFEINE AND BUBBLES: ULTRASOUND AS A PERMEATION ENHANCER

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Introduction: This study is part of a larger project which aims to assess the safety and effectiveness of formulations containing bubbles and caffeine, stimulated by the application of ultrasound for treating cellulite. One of the proposed security tests is the phototoxicity in vitro. The bubbles are miscellar compounds of lipids complexed with polyethylene glycol (PEG) containing gas inside. The ultrasound breaks up the “bubbles”, and was used with the aim of improving the availability of caffeine. The bubbles have interesting delivery features, but there are scarce studies of topicality and cosmetic application. Methods: Phototoxicity was performed using Balb/c 3T3 fibroblasts cultivated with DMEM medium supplemented with 10% fetal bovine serum. The cells were plated at 96-well plates with 20000 cells per well. Samples of bubbles and caffeine were added in eight 1:47 dilutions, in two separate plates, followed by the guidelines of the OECD 432 (2004). One of the plates was exposed to 5 J/cm2 UVA radiation, whereas the other plate was kept, under the same conditions, but without the ligh. The phototoxicity was assessed using the vital dye Neutral Red (NR). Results and discussion: The calculations classified both substances as non-phototoxic at the concentrations tested, caffeine PIF = 1 and MPE = -0.018, “bubbles” PIF = 1 and MPE = -0.29 and “bubbles” added ultrasound PIF = and MPE = -0.198, according to OECD parameters which predicts that non-phototoxic substances have a PIF < 2 and MPE < 0.1. Conclusion: Based on these promising results the tests of safety and effectiveness will be continued.
HOW THE HIALURONIC ACID INFLUENCES THE ABSORPTION AND BIOAVAILABILITY OF NANOSTRUCTURED SYSTEMS? A SYSTEMATIC REVIEW

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Introduction: Hyaluronic acid (HA) is a biodegradable, biocompatible and nontoxic biopolymer with excellent mucoadhesive and viscoelastic properties that has been explored in several areas of medicine, including nanoparticle drug delivery systems. From this, the objective of this work was to perform a systematic review in order to verify the influence of HA on the absorption and/or bioavailability of drugs carried in nanostructured systems in formulations intended for systemic use. Methods: The investigation were conducted in March 2017 using Pubmed, Web of Science and Scopus databases, applying descriptors related to “nanoparticles”, “hyaluronic acid”, “biological availability” and “pharmacokinetics” combined in the search strategy. It was based on the methodology proposed by Cochrane and PRISMA recommendations. Results and discussion: 41 in vitro and/or in vivo experimental studies on HA containing nanoparticles containing assays related to absorption and/or bioavailability of HA nanoparticles were included. The wide use of HA as nanocarriers has been evidenced, presenting it as a coating agent, matrix component or complexed to the drug, associated with a great variety of drugs, especially antitumor drugs. It was shown to be effective in increasing permeation in assays that simulated intestinal mucosal uptake, and also in triggering of slower and more sustained in vitro release rates when compared to non-HA formulations, in addition to improve bioavailability of drugs in the plasma circulation. Conclusions: It was verified that the HA conferred benefits related to in vitro release, absorption and bioavailability to the nanocarriers, evidencing its relevance in nanotechnology, for the improvement of the therapeutic effect.

Acknowledgments: to Fundação Araucária and CAPES.

DEVELOPMENT AND PHYSICA-CHEMICAL CHARACTERIZATION OF DERMATOLOGICAL NANOEMULSIONS CONTAINING FIXED OIL OF WILD PASSIONFRUIT

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Introduction: Nanoemulsions are widely employed as topical carrier systems because of its more efficient penetration in human skin. Due to its biocompatibility and low toxicity, vegetable oils can be applied as excipients or actives substances in nanoemulsions. However, wild Passiflora fixed oils are underused in dermatology, leading to novel studies. This study aimed to develop O/A nanoemulsions containing Passiflora cincinnata fixed oil, variety BRS Sertão Forte, provided by EMBRAPA. Methods: The oil was analyzed by gas chromatography to determine fatty acids composition and also in vitro cytotoxicity assay in HaCat keratinocytes by resazurin colorimetric test. The nanoemulsions were composed of 15% oil, 8.7% sorbitan monooleate, 1.3% polysorbate 80, 5% glycerol and 70% water, obtained by sonication for 20 minutes and characterized by the droplet size, polydispersity index, zeta potential and physicochemical properties during 90 days of storage. Results and discussion: The fatty profile revealed mainly linoleic acid (73.72%). The oil was not cytotoxic in concentrations up to 100µg/mL. The nanoemulsions were evaluated on days 1 and 90, respectively, according to following parameters: droplet size 225.70 ± 3.65nm e 305.00 ± 8.11nm; polydispersity index 0.276 ± 0.01 e 0.316 ± 0.02; zeta potential -40.40 ± 0.36mV e -45.20 ± 0.58mV, electrical conductivity 165.83 ± 2.17µS/cm e 181.40 ± 1.02µS/cm; turbidity 16.50 ± 1,05NTU and 22.60 ± 1,22NTU; pH 6.32 ± 0.21 e 6.14 ± 0.20. Conclusions: The statistical variations were significant (p
DEVELOPMENT OF ETHYLCELLULOSE MICROPARTICLES CONTAINING PRAZIQUANTEL

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Introduction: The preparation of microparticles containing praziquantel (PZQ) by emulsion solvent evaporation technique is an alternative to improve the drug stability and mask the bitter taste, aiming the development of new oral dosage forms. Methods: The microparticles were prepared by a factorial design of $2^3 + 2C$ defined in levels of -1, 0 and +1 wherein the ratios of the independent factors composed for ethylcellulose (EC) were optimized: PZQ and Tween 80 were 1.5%, 1.0% and 1.5% (w/w). The preparation of eight formulations, controls (F1, F2, F3, F4, F6, F7, F8 and F9) and two central-point formulations (F5 and F10) were accomplished using two stirring techniques (mechanical and magnetic) at 800 rpm. Then, they were submitted to vacuum filtration, dried in desiccator, and stored with light protection. To characterize the microparticles, the macroscopic analysis, scanning electron microscopy, particle size analysis and the yield were studied. Results: The formulations prepared using magnetic stirring displayed better yield for F8 (98.4%), justified for the ratios of Tween 80 and PZQ at 1.50% and 1.25% (w/w). The high porosity observed could be an indicative that taste masking can be achieved. The ideal proportion of PZQ and Tween 80 was found to be 1.50% (w/w), providing yields higher than proportions of 1.25% and 1.0%. The mechanical stirring was more suitable compared to the magnetic to obtain microparticles with size and regular surface area although magnetic stirring process showed higher yield.

L-ASPARAGINASE ENCAPSULATION INTO PERMEABLE POLYMERSOMES

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Introduction: L-asparaginase is an enzyme used in the treatment of acute lymphoblastic leukaemia. This enzyme catalyses the hydrolysis of L-asparagine, which is essential to cancer cells. Since the direct administration of L-asparaginase is associated with various side effects besides the enzyme inactivation by proteases and antibodies, its nanoencapsulation was studied as a means of improving stability, bioavailability and biocompatibility. More specifically, this work aimed to develop polymeric nanovesicles (polymersomes) permeable to L-asparagine, while keeping the enzyme encapsulated and protected against a hostile environment. Methods: L-asparaginase permeable polymersomes were obtained by the film-hydration method, mixing two different copolymers: PMPC®-PDPA70 (poly((2-methacryloyloxy) ethyl phosphorylcholine)- block-poly (2-(diisopropylamino) ethyl methacrylate), which forms robust membrane, resistant to interaction with plasma proteins; and PEO15°PBO25 (poly(ethylene oxide)-block-poly(butylene oxide), which forms thin membranes, permeable to small polar molecules. L-asparaginase was encapsulated through electroporation and non-encapsulated enzyme was removed by size-exclusion chromatography. The nanovesicles were characterized using dynamic light scattering, transmission electron microscopy and high-pressure liquid chromatography. Results and discussion: PMPD-PDA polymersomes containing a small PEO-PBO bud were obtained, having an average mean diameter of 112-120 nm and PdI of 0.17-0.20. Electroporation did not cause any changes to the nanovesicles size and shape. L-asparaginase was successfully encapsulated with loading efficiencies of 600-1600 molecules per polymersome. Conclusions: The obtained polymersomes have potential to be used as L-asparaginase nanocarriers, protecting the enzyme against proteases and minimizing side effects. Further studies regarding L-asparaginase permeation are under development.

Financial support: This work was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).
POLY(ANHYDRIDE) NANOPARTICLES CONTAINING CASHEW NUT PROTEINS CAN INDUCE A STRONG TH1 AND TREG IMMUNE RESPONSE AFTER ORAL ADMINISTRATION

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Introduction: Cashew nut allergy is the second most commonly reported tree nut allergy. Traditional allergen immunotherapy presents several clinical drawbacks that can be reduced by using nanoparticles-based allergen-delivery systems, modulating the immune response towards a protective one. In this context, the goal of this work was to assess the potential of poly(anhydride) nanoparticles (NP) for cashew nut oral immunization. Methods: Cashew nut allergens-loaded nanoparticles (CNE-NP) were prepared by solvent displacement method. After nanoparticles characterization, oral immunomodulation ability was evaluated in BALB/c mice (experiments were performed in compliance with the regulations of the Ethics Committee of the Gonçalo Moniz Institute, Oswaldo Cruz Foundation - FIOCRUZ in line with the Brazilian legislation on animal experiments, approved protocol 008/2015). Results and discussion: Our results demonstrated that CNE-NP induced a higher Th1/Th2 ratio in comparison with animals immunized with free cashew nut proteins. Indeed, a decrease in splenic Th2 cytokines (IL-4, IL-5, and IL-13), and an enhancement of pro-Th1 (IL-12 and IFN-γ) and regulatory (IL-10) cytokines was observed. Furthermore, mice orally immunized with CNE-NP presented an increased expansion of CD4+ T regulatory cells, such as CD4+Foxp3+ and CD4+LAP+, in the mesenteric lymph nodes. Conclusions: In conclusion, oral immunization with a single dose of poly(anhydride) nanoparticles loaded with cashew nut proteins led to a pro-Th1 and Treg immune response. Furthermore, their immunomodulatory properties could be introduced as a new approach for management of cashew nut allergy.

Acknowledgements: The authors are grateful for Ph.D scholarship and PDSE 6651-15-1 from the Brazilian Education Ministry (CAPES) and Foundation of Research and Technology Development of the State of Pernambuco – FACEPE (AMD #0021-2.00/17). This work was also supported by the Brazilian Ministry of Science and Technology - MCTI (SisNANO/LARNano-UFPE, CNpq # 402282/2013-2) and FACEPE (APQ #0361-4.03/14).

DEVELOPMENT OF A BIODEGRADABLE DELIVERY SYSTEM CONTAINING CIDOFOVIR TO TREAT RECURRENT RESPIRATORY PAPILLOMATOSIS

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Introduction: Recurrent Respiratory Papillomatosis (RRP) is a chronic disease caused by HPV and affects mainly children and teenagers. In order to remove the laryngeal lesions several surgical interventions might be performed along with antiviral drugs association, e.g. cidofovir (CDV), to control the disease. Intralesional injection of CDV, however, shows reduced bioavailability, since an important amount of the drug extravasate to the blood stream and surrounding tissues. The aim of this project was the development of a biodegradable release system composed of a suspension of microspheres based on a blend of HPMC K100 and carbopol 940 containing CDV, in order to prolong its permanence at the site of action. Methods: MEs were produced by the simple emulsification method followed by solvent evaporation, and were characterized in vitro by zeta potential, size distribution, drug encapsulation content, scanning electron microscopy and thermal analysis and in vivo. Results: in vitro studies showed absence of incompatibilities between the drug and the polymers and adequate morphological characteristics. The in vivo studies showed biocompatibility and absence of toxicity of the developed systems, through histological analysis and the chorioallantoic membrane assay. CDV and the MEs were radiolabeled with technetium-99m in order to compare and confirm the adhesion of the particles after local injection in the vocal folds for a longer time in relation to the CDV solution. Conclusion: MEs were suitable for encapsulating CDV, showed biocompatibility and prolonged adhesion in vocal folds, which is a promising alternative in the treatment of RRP.

Acknowledgements: CNpq, Capes, Fapemig

DEVELOPMENT AND EVALUATION OF ANTIFUNGAL ACTIVITY OF MUCOADHESIVE ORAL MEMBRANE CONTAINING INCLUSION COMPLEX OF THYMOL INTO HYDROXYPROPYL β- CYCLODEXTRIN

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Introduction: The thymol (TM) is recognized for exhibiting strong antifungal activities against a wide range of pathogenic microorganisms. However, this compound present limitations with their high volatility and low solubility in aqueous medium. The aim of this study was to develop and characterize mucoadhesive oral membrane containing inclusion complex of TM with hydroxypropyl-β-cyclodextrin (HPβ-CD) and investigate in vitro antifungal activity against species Candida. Methods: Membranes were obtained from a solution containing 1.5% of chitosan (CTS) in acetic acid (w/v) by solvent evaporation method after incorporation of inclusion complexes of TM with HPβ-CD in molar ratios of 1:1. The combination of CTS with TM/HPβ-CD was analyzed by swelling capacity, differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and drug content by high performance liquid chromatography (HPLC). After this, were investigated of antifungal activity against several strains of Candida albicans ATCC 18804 and clinical isolates of C. krusei 43 and C. parapsilosis RL 101 using the broth microdilution technique. Results and discussion: The swellability membranes indicated that the presence of the complexes decreased the swelling profile of chitosan. The DSC curves showed absence of endothermic peak in the temperature range of TM volatilization. The SEM images revealed the presence of complexes formed in membranes. The average percent TM content of the membranes was of 60%. The formulations showed antifungal activity with minimum inhibitory concentrations (MIC) ranging between 250 to 1.015 µg/mL. Conclusions: Results showed that these systems containing complexed TM demonstrated to be an promising alternative for the treatment of oral candidiasis.

THERMOSENSITIVE LIPOSOMES CONTAINING GADODIAMIDE: PREPARATION, CHARACTERIZATION, AND PRELIMINARY EVALUATION OF THEIR STABILITY AND THERMOSENSITIVITY

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Gadodiamide (Gd-DTPA-BMA) is a gadolinium contrast, used in magnetic resonance imaging (MRI). This complex also can induce the apoptosis of neoplastic cells through activation of caspase-3. Several studies have reported the encapsulation of Gd-DTPA-BMA in liposomes for MRI purposes. On the other hand, only a few have explored their potential for cancer treatment. In this context, thermosensitive liposomes constitute promising nanocarriers, since they may contribute to increased treatment efficacy due to the association with hyperthermia techniques. The proper choice of the lipid composition can influence the physicochemical characteristics of the vesicles, and thus, affect the treatment efficiency. Therefore, the aim of this study was to develop, characterize and compare different liposomes containing Gd-DTPA-BMA: (i) traditional thermosensitive liposome (TTSL-Gd); and (ii) thermosensitive liposome containing lysophospholipid (LTSL-Gd). The formulations were prepared by lipid film hydration and extrusion method. The size and polydispersity index (PDI) were determined by dynamic light scattering (DLS). The zeta potential (ζ) was determined by DLS associated with electrophoretic mobility, at pH 7.4 in angle of 90°. Gd-DTPA-BMA entrapment was determined by hydrophilic interaction liquid chromatography. The storage stability, was evaluated at 0, 7, 15 and 30 days after preparation. Morphological examination was performed by means of transmission electron microscopy. The thermosensitivity was assessed by DLS (heating range: from 37 °C to 45 °C; heating rate: 1 °C/minute). No significant changes in size, PDI, ζ, and Gd-DTPA-BMA entrapment were observed during the storage period evaluated, for both formulations. The morphological analyses showed the presence of spherical unilamellar vesicles with homogeneous populations (PDI < 0.3), presenting size of less than 150 nm. Negative zeta potential values, close to neutrality, were observed in both formulations. The preliminary thermosensitivity study demonstrated that the lipid composition chosen for formulations was adequate, since Lβ → Lα phase transition temperature values (TTSL-Gd: 41°C; LTSL-Gd: 40°C) are compatible with the moderate hyperthermia. The results demonstrated that both formulations were successfully prepared, characterized, and presented suitable features for future in vitro studies.

Acknowledgments: CAPES, CNPq, FAPEMIG, and Center of Microscopy of UFMG.
PRE-FORMULATION STUDIES OF A PEG-30 CASTOR OIL BASED MICROEMULSION

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Introduction: Microemulsions (ME) are colloidal systems that have been used to enhance solubility and oral bioavailability of poor water-soluble drugs. PEG-30-Castor-Oil, a non-ionic surfactant derived from the Ricinus communis oil, has not been reported as a stabilizing agent for ME. The aim of this work was to develop PEG-30-based ME and evaluate their physicochemical stability. Methods: First, a pseudoternary phase diagram was carried out by the titration methodology. A PEG-30-Castor-oil/Span®-80 ratio was chosen based on the oil hydrophilic-lipophilic balance. Afterwards, the droplet size, the polydispersion index (PDI), the zeta potential (NanoZS, Malvern®), the conductivity (CG 2000, Gehaka®) and the pH (PG 1800, Gehaka®) of the selected microemulsion were measured during 30 days (triplicate). Results and discussion: The ME were translucid and their average droplet size has slightly increased during the study from D1 (21.8 ± 0.3 nm) to D30 (24.5 ± 0.3 nm) (ANOVA + Post-hoc Tukey; p>0.05). Conclusion: This work reveals the ability of PEG-30-Castor-oil to produce ME that can be stable up to 30 days. Thus, the samples will be evaluated up to their de-stabilization and new batches including the addition of poor water-soluble drugs will be later produced. Acknowledgement: CAPES and CNPq (438474/2016-3) for financial support.

DEVELOPMENT AND CHARACTERIZATION OF LEFLUNOMIDE BIODEGRADABLE INTRAOCULAR IMPLANTS AIMING THE TREATMENT OF OCULAR NEOVASCULARIZATION

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Introduction: Pathological neovascularization is the leading cause of blindness in a wide range of ocular diseases such as age-related macular degeneration. Conventional treatment for this condition is intravitreal injection containing anti-VEGF biologic drugs, however, the repeated and long-term injections of these agents are being associated with severe ocular impairment. Leflunomide (LEF) is a well-known immunosuppressive and anti-inflammatory prodrug that recently exhibited an anti-angiogenic activity in different carcinomas studies. Therefore, the aim of this work was to develop an intravitreal biodegradable implant containing LEF for the local treatment of ocular neovascularization. Methods: LEF implants were prepared and characterized by thermal analysis techniques, differential scanning calorimetry, infrared spectroscopy and scanning electron microscopy. The quantification of LEF released from implants was performed using HPLC–UV analysis. The anti-angiogenic activity was investigated using the chick embryo chorioallantoic membrane (CAM) in vivo model. Results and discussion: The implants characterization showed that the drug and the polymer were thermally stable during the molding process and indicated a possible interaction between them after lyophilization. Nevertheless, this interaction was not detrimental to the system and allows one reproducible and prolonged release of LEF from implants for 6 weeks. CAM assay results indicated that LEF implants provided a significant decrease of 29.7% blood vessels density compared to the control. Conclusion: The results indicated that LEF biodegradable implants were able to provide a prolonged release of the drug and also to inhibit the angiogenic process. Therefore, can be a potential intravitreal drug delivery system for the treatment of ocular neovascularization.
SWELLING PROPERTIES OF LIPID NANOPARTICLES-HYDROGELS HYBRID SYSTEMS FOR NYSTATIN DELIVERY

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Hydrogel-based delivery matrices have been designed and fabricated to fulfill the ever-increasing needs of the pharmaceutical and medical fields. The combination of two distinct delivery platforms, nanoparticles and hydrogel, allows the hydrogel network properties to be independently tailored for adhesion while maintaining controlled and prolonged. In this work, lipid nanoparticles (LN) was embedded into hydrogel network by mixing with monomer solution, followed by gelation. The chemically (glutaraldehyde (A) or trimetaphosphate (B)) and physically (C) crosslinked PVA-hydrogels were prepared with LN and Nystatin was incorporated into the system. Swelling kinetics such as swelling ratio (SR), transport exponent (n) was determined. Dynamic swelling measurements were made by gravimetry. The amount of Nystatin was measured by spectrophotometry. The n was calculated by plotting data log Mt/M vs. log t using linear regression. The A had the highest SR in time-dependent swelling behavior, whereas the SR of B had the lowest. The n values of A, B, and C are 0.51, 0.33 and 0.42, respectively. These values clearly indicate a difference on the swelling mechanism. The diffusion was Fickian in nature for A, and Less Fickian for B and C. The Nystatin release profile showed a continuous and controlled behavior. The study revealed a considerable difference in the mechanism of water transport, which is probably due to the difference in the molecular structure of hydrogels. The above difference in behavior is of considerable importance in controlled release applications.

DEVELOPMENT, CHARACTERIZATION AND EVALUATION OF LOCAL DELIVERY SYSTEM (LDS) CONTAINING COPAIBA OIL (CO) FOR CHRONIC PERIODONTITIS

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Introduction: Chronic periodontitis is an infectious disease leading in inflammation of the tissues that support the teeth. Treatment consists of removal and control of the biofilm and use of antimicrobials agents. Metronidazole (MTZ) is the most used however systemic use of antibiotics has not been recommended in recent years because of various disadvantages such as inadequate concentration of the drug. Local delivery system (LDS) would be an alternative to promote greater retention, drug dosage control and prolonged release. Copaiba oil (CO) have shown promising effect on inhibition of the main bacteria present in biofilm. This study aimed the production and characterization of a polymeric film with MTZ and CO as a complementary therapy. Methods: Films were developed by the solvent casting technique with different concentrations of polymers chitosan (CH: 3-6%) and gelatin (GL: 4-7%), MTZ (Base and Benzoate), CO (1.5; 3 and 4.5%). In vitro release studies were used for selecting the best proportion of polymers in formulation. They were performed in SR6 Flask Dissolution Test Station. The best LDS were charactherized by Weight, % Moisture, Thickness and Mechanical Properties. Results and discussion: LDS containing CH 6%, GL 4%, MTZ and CO 1.5% shows the better release profile, with prolonged release of MTZ. Characterization results showed weight (0.332±0.043g), % moisture (17.72), thickness (0.014±0.001mm), force (45.984±6.899N), strain (2.913±1.438) and stress (457.329±83.18MPa). Conclusion: The formulation developed with CH 6%, GL 4%, MTZ and CO 1.5% is a promising LDS for treatment of chronic periodontitis. Financial support: CAPES and FAPERJ
DEVELOPMENT OF INHALER IBUPROFEN FOR SYSTEMIC EFFECT

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Introduction: A drug commonly used for pain relief is ibuprofen (IBF), which when administered intravenously works to relieve even more intense pain and immediately. There is a growing trend towards the development of inhaled drugs that generate systemic effect through easy absorption of drugs into the lung alveoli. The IBF dry powder inhaler (DPI) has been developed for systemic effect for immediate pain relief, without invasive administration, which can even be self-administered. Methods: The formulation was developed with the micronization of the active in mill crushers in the presence of lactose inhaler as the carrier. In the evaluation of the performance, the uniformity of released dose and aerodynamic distribution of particles (ADP) tests were performed. Results and discussion: Micronization of the active was efficient and generated particles with an average diameter around 3.0 μm (2.93 ± 0.17 μm and 2.60 ± 0.43 μm), an adequate value for inhalation formulations intended for systemic effect. Physico-chemical tests show that ibuprofen DPI releases the drug with adequate content uniformly, in addition the aerodynamic distribution of its particles (ADP) is similar to the commercially available DPI drugs, whose values obtained from the fine fraction of particles, medium diameter and geometric standard deviation were, respectively, 22.04%, 6.15 μm and 1.69. In vivo-in vitro evaluation, performed by the ADP test, revealed that the IBF was deposited in the alveoli to effect a systemic effect. Conclusions: This work contributes to the reference of studies on the development and analysis of DPI drugs for systemic effect, as well as to demonstrate the application of the performance methods developed to evaluate this pharmaceutical form, in addition IBF DPI has potential to be medicine which relieves severe pain immediately and non-invasively.

ID: 428

QUANTUM DOTS AS A CARRIER SYSTEM FOR MONOCLONAL ANTIBODY: EVALUATION OF EFFECTIVENESS AND BIOSAFETY

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Introduction: Inflammatory processes present in retinal diseases cause abnormal proliferation of blood vessels, which damages physiologically and anatomically the retinal structure, causing rapid and irreversible vision loss. For the treatment of these diseases, novel delivery systems aim to favor local administration of anti-neovascularization drugs and to provide a prolonged action within the eyeball. With this view, a nanoparticulate quantum dots (QD) system was developed for the delivery of bevacizumab, and the present work had as objective to evaluate its efficacy and biosafety in vivo. Methods: The system was obtained by aqueous synthesis (Mansur et al., 2015), the particles were stabilized with chitosan and functionalized with bevacizumab. The two systems obtained (QD-Beva and QD-Control) had their anti-angiogenic activity verified on chorioallantoic membrane (CAM). For the biosafety assessment, 5 μl of the samples were injected intravitreally in male Wistar rats, and these were monitored by electroretinogram (ERG) for 28 days (CEUA 107/2018). At the end of this period, histological ocular slides were evaluated for the maintenance of the retinal structure. Results and discussion: The quantification of neovascularization indicated that the bevacizumab action was maintained in higher concentrations of the system. During the 28-day follow-up, there were no significant changes in the characteristic waves of ERG, suggesting preservation of the physiological functions of the retina. Histological analysis showed preservation of the retina structure. Conclusions: QDs showed to be a safe and effective system for intravitreal anti-neovascularization drugs, presenting potential for application in the treatment of diseases in the retina. Acknowledgements: The authors thank to CAPES and CNPq for financial support.
EVALUATION OF PHOTOPROTECTIVE AND ANTIOXIDANT POTENTIAL OF BRAZILIAN NUT SHELLS EXTRACTS: DETERMINATION OF TOTAL PHENOLICS AND PHOTOTOXICITY

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Sunscreens (SNS) protect skin against solar radiation and prevention of photoaging, skin cancer and solar erythema. Antioxidant agents in SNS may protect against UV-induced free radicals production and damage and may potentiate action of UV filters. Brazilian nut shells are residues of Amazonian fruits with an antioxidant potential and may be used as a sustainable raw material for cosmetic products since this material is frequently discarded. However, its efficacy and especially safety and photosafety should be guaranteed. This study proposes evaluation of total phenolics and phototoxicity potential for Brazilian nut shells extracts as a potential new ingredient for SNS. The extract was obtained by maceration of raw material for 4 h and 72h in ethanol:water (70:30) and dried by lyophilization. Total phenolic content was determined by Folin-Dennis method and was expressed as mg of gallic acid equivalents (GAE) per 1g of extract. The phototoxicity potential of the extracts were evaluated using 3T3 fibroblast cultures that were subjected (or not) to irradiation according to OECD TG 432. Total phenolic content of Brazilian nut shells extracts were 37.49 and 50.04 mg GAE/g extract, for 4 h and 72h of maceration process, respectively. The in vitro phototoxicity test showed that both extracts present phototoxic potential (MPE > 0.015) and thus future steps will involve future liquid-liquid solvent separation with solvents of different degrees polarities to find the best fractions for photoprotective potential and the ones involved in phototoxic potential.

EFFECT OF PREFORMULATED EXCIPIENT ON THE DISSOLUTION RATE OF CALCIUM ATORVASTATIN CAPSULES

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Introduction: Calcium atorvastatin (ATC) is one of the most commonly used drug in the treatment of dyslipidemia. Compounding preparation of capsules containing ATC has often been requested due to be a high-cost medicine. ATC presents low solubility and high permeability; therefore adjuvants substances are able to interfere on its solubility. The aim of this study was to evaluate the effect of a preformulated excipient on the dissolution rate of ATC capsules of different dosages. Methods: The flow properties of the ATC and an excipient prepared according three pharmacies were determined, which was constituted by colloidal silicon dioxide, calcium carbonate, magnesium stearate, microcrystalline cellulose and lactose monohydrate. Hard capsules with 10, 20, 40 and 80 mg were prepared using two different sizes of gelatin shells (Formulations A-H). Results and discussion: The results indicated that the excipient presented appropriate characteristics to aid in the encapsulation procedure, since all batches were approved in relation to the weight variation. Dissolution data were obtained from the spectrophotometric quantification at 242 nm and shown that only the formulation F (20 mg at capsule size 3) achieved the recommended dissolution rate. This may be attributed to the features of the excipient which although aided in encapsulation did not promote dissolution as desired for all dosage forms. Conclusions: It is suggested to reduce hydrophobicity by replacing calcium carbonate with sodium bicarbonate to maintain the prevention of ATC lactonization. Moreover, wetting agent as sodium lauryl sulfate and disintegrating agent as sodium starch glycolate could be added. Financial support: PROPE-UFSJ.
PREPARATION OF NISTATIN MONTHWASH FOR THE MANAGEMENT OF ORAL COMPLICATIONS ARISING FROM ONCOLOGICAL TREATMENT

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Introduction: Candidiasis is one of the most frequent opportunistic infections in patients undergoing oncological treatment. Nystatin is among the therapeutic agents used in the management of oral mucositis in patients with fungal cell membrane. All oral liquid pharmaceutical dosage forms with nystatin present ethyl alcohol and other adjuvants that origin discomfort causing low compliance to treatment. The aim of this work was to propose a suspension formulation containing nystatin for using as mouthwash for the management of oral complications arising from oncological treatment. Methods: Compositions of six oral suspensions were analyzed, among which two were submitted to physicochemical determinations (pH and relative density). These criteria were applied for stablished of the proposed formulation (PF) constituted by nystatin, disodium EDTA, sodium metabisulfite, methylparaben, propylparaben, propylene glycol, hypromellose, simethicone, sucralose, pineapple flavor and purified water. After preparation, PF was packed in amber glass bottle with head space (50%), stored at around 25°C and submitted monthly to assays according to Brazilian Pharmacopeia during 180 days. Results and discussion: The results indicated that PF presented as a deflocculated suspension, maintaining pH and relative density throughout the study. However, it was found significant decrease in the amount of nystatin in PF after 60 days probably due to the formation of tightly packed sediment that probably impaired the content uniformity. Conclusions: A 30-day shelf life can be assumed for the compounding preparation. Nevertheless, it would be interesting to control the flocculation to prevent the caking phenomenon, since this problem affects the sedimentation rate. Financial support: PROPE-UFSJ.

PREPARATION AND MONITORING OF BEHAVIOR OF COMPOUNDING SYRUP CONTAINING CYPROHEPTADINE CHLORIDE

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Introduction: The use of oral liquid dose forms with cyproheptadine hydrochloride (CHD) as appetite stimulator is common for children. The aim of the study was to prepare and monitor of behavior of compounding syrup containing CHD. Methods: The studied formulation (SF) was based on a medicine prescription (MP) containing Ad-til® (10 mL), Redoxon® (20 mL), CHD 2 mg/5 mL (120 mL), lactic acid (10 mL) and syrup to 200 mL. Ingredients from four liquid industrial products (LP) containing CHD were considered. MP and one of the LP were analyzed in relation to organoleptic properties, pH and relative density. The SF was prepared and evaluated for 180 days. CHD determination into SF was carried out by spectrophotometry at 286 nm using acid aqueous medium. Results and discussion: It was noted that MP became a heterogeneous system due to lipophilic vitamins from Ad-til®. Redoxon® was diluted and lactic acid brought the pH to 2.9. However, CHD is the most important agent of preparation so that the SF had the pH adjusted to 4.0 as key element on its stability. Additionally, Ad-til® and Redoxon® were excluded of the SF. Concentrations above 90% of CHD were found during 120 days both 24°C and 40°C. Results of organoleptic properties, pH and relative density showed no changes during the study. Conclusions: It could be said that MP presented physical and physicochemical problems able to compromise its stability. The SF presents wide potential to be prescribed as compounding formulation. Financial support: FAPEMIG and PROPE-UFSJ.
PREPARATION AND EVALUATION OF TOOTH GEL TO CANCER PATIENTS

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Introduction: Cervical-facial radiotherapy causes innumerable sequels in the irradiated patient, being systemic or restricted to the oral environment. The oral mucosa of these individuals is profoundly compromised by radiotherapeutic treatment with or without chemotherapy, presenting several complications. Dentifrices containing sodium laurel sulfate (SLS) cause damage to these patients, as they lead to dryness of their mucosa. The purpose of this work was to develop a dentifrice capable of minimizing xerostomia related to oral mucosa associated to a less abrasive profile, which was intended for hygiene, prevention of caries, control of dental biofilm, and tooth sensitivity in cancer patients. Methods: The qualitative composition and physicochemical characteristics of nine commercially available dentifrices and a compounded formulation were analyzed, which enabled the preparation of the proposed formulation (PF) constituted by sodium fluoride equivalent to 1500 ppm of active fluoride, poloxamer 407, triclosan, sucralose, colloidal silicon dioxide, potassium nitrate, methylparaben, propylparaben, propylene glycol, raspberry flavor, xanthan gum, and purified water. PF was packed in white HDPE tubes, stored at room temperature (24 ± 2 °C), relative humidity of 60 ± 5% and analyzed periodically for 180 days. Results and discussion: Spreadability results not only indicated adequate PF behavior in relation to the packaging and storage conditions but also revealed the need to raise the propylene glycol concentration in PF to avoid the occurrence of syneresis after 60 days. Further, pH data showed that PF is compatible with the pH of oral homeostasis and values above the critical pH, avoiding the occurrence of dental demineralization. Conclusions: It is suggested that the PF has a peculiar composition and physicochemical quality to be used as a suitable dentifrice for patients undergoing anticancer therapy. Financial support: PROPE-UFSJ.

CHARACTERIZATION OF CLAY FROM THE SOUTHWEST REGION OF DIVINÓPOLIS-MG

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Introduction: Clays are composed of aluminum silicate minerals of macroscopic dimensions and laminar formations associated with oxides presenting specific therapeutic properties. Several factors indicated that a material found in favorable geographical location could be black clay. The aim of this study was to characterize a sample of clay extracted in the Southwest region of Divinópolis-MG. Methods: The material investigated as black clay (BC) was subjected to Fourier transform infrared spectroscopy (FTIR) and gray clay (GC) was used as the reference standard. The sample was also analyzed for pH, solubility, loss by desiccation, and chemical analysis by determination of inorganic compounds by determination of oxides (SiO₂, Al₂O₃, MgO, FeO, CaO and TiO₂). Results and discussion: The FTIR spectrum revealed stretches at wavelengths expected and similar to GC, in addition to several bands that were attributed to the organic composition peculiar to the nature of the material. Factors such as depth of extraction (5 m), color, odor, low shine, ease of modeling evidenced to be clay. The BC presented very soluble, pH 5.8 and about 32% water. Size distribution by sieving showed particle size less than 180 μm, being classified as fine powder. The chemical analysis revealed that the BC presented lower SiO₂, MgO, FeO and CaO contents than GC, Al₂O₃ higher than GC, whereas TiO₂ was found only in BC. Conclusions: It is suggested that the material analyzed is clayey and may be classified as gray clay with low purity. Financial support: FAPEMIG and PROPE-UFSJ.
**EVALUATION OF SAFETY AND EFFICACY OF GRAPE POMACE (Vitis labrusca L.) FROM WINEMAKING PROCESS AS ANTIOXIDANT RAW MATERIAL FOR COSMETIC FORMULATIONS**

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**Introduction:** Grapes have a great number of antioxidants in their chemical composition. Grape pomace from the winemaking process is also a rich source of phenolic compounds and fibers and may be considered a potential source of raw cosmetic materials. The goal of this study was to investigate the safety and the efficacy of grape pomace (Vitis labrusca L.) obtained from winemaking process as antioxidant raw cosmetic materials. **Methods:** Grape pomace was dried and submitted to extraction with 75% acetone-water, at 80 °C, for 2 h. The extract was filtered and freeze-dried. The safety and efficacy of the extract from grape pomace were tested on fibroblasts (3T3 cell line). The safety was evaluated by cytotoxicity assay (MTT) and the morphology of the cells was analyzed by Scanning Electron Microscopy (SEM). The efficacy was evaluated by cytoprotection assay (H2O2). **Results:** Results of cytotoxicity showed that the extract from grape pomace were safe even in the highest concentration tested (200 mg.mL-1) against 3T3 cell line. SEM analysis revealed that there were no morphological cell changes of cells treated. Cytoprotection of cells towards the oxidation promoted by the peroxide solution was observed in the lowest concentration tested (0.73 mg.mL-1). **Conclusion:** The safety and efficacy of the extract from grape pomace as raw material for cosmetic formulations was proposed through cell culture assays.

**THE USE OF GRAPE RESIDUE FOR THE DEVELOPMENT OF EXFOLIATING AND ANTIOXIDANT COSMETIC PRODUCTS**

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**Introduction:** The ban on the use of microplastics in USA and Canada in exfoliating cosmetics shows the tendency to replace them with natural (biodegradable) ingredients. During the processing of the wine an expressive amount of residues is generated from the grapes, which are a source of fibers and phenolic compounds discarded by the wine industry. The objective of this study was to evaluate the antioxidant activity of grape pomace and its application as a natural exfoliating cosmetic ingredient. **Methods:** Grape residue (Vitis labrusca cv Bordo) was dried at 60°C for 2 hours and submitted to extraction with acetone, acetone-water 75%, methanol, methanol-water 75%, ethanol and ethanol-water 75% at 60° C. The extracts were filtered and lyophilized for further evaluation of total phenolic content and antioxidant activity by DPPH radical scavenging. Grape pomace was sieved and incorporated in an exfoliating formulation. **Results and discussion:** The extraction carried out with 75% acetone-water showed a better yield (1.9 g.g-1) when compared to the other solvents tested. Freeze-dried extracts obtained with acetone-water revealed a high total phenolic 69.830 mg GAE g-1content and HPLC analysis confirmed the presence of ellagic acid as an active bio-compound. Antioxidant activity determined by the DPPH method revealed there was no statistical difference between the extract (EC50 6.9±0.21) and BHT (EC50 7.6±0.71). **Conclusion:** The formulation containing grape pomace as natural and sustainable ingredient demonstrated a satisfactory aspect as exfoliating agent beside an additional antioxidant activity.
IMPACT OF DIFFERENT TENSOACTIVES ON THE MORPHOLOGY OF PLA-b-PEG MICROCAPSULES LOADED WITH PERILLYL ALCOHOL

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Introduction: Perillyl alcohol (POH) is a natural compound that has attracted a significant interest due to its potent antitumor activity. However, clinical trials have exhibited poor tolerance by oral administration. The entrapment of POH into polymeric shell by emulsion solvent-evaporation process may be an alternative delivery platform. However, such process is strictly dependent of the employed tensoactive and its concentration. In this way, the influence of poly(vinyl alcohol) (PVA) and sodium cholate (SC) on the shear strength and morphology of POH particles were evaluated. Methods: PLA-b-PEG copolymer and emulsion solvent-evaporation process were choosing to entrap POH. Based to the ability of tensoactives to stabilize the water/chloroform interface, was selected the following amounts of PVA and SC: 0.01% and 0.04% for both, 1.0% (PVA) and 1.5% (SC). Nile Red was incorporated in the polymeric shells for confocal images. Pendant drop method was used for interfacial tension measurements. Results and discussion: Sphericity was only attained above an SC content of 0.04%. Comparatively, PVA was able to generate spherical-shape even at 0.01%. Under centrifugation only particles with PVA was able to maintain the morphology, demonstrating its potential to enhance stability. Interestingly, above the CMC’s concentration only the samples formulated with SC (1.0%) maintained sphericity after shear strength. The entrapment efficiency was 63 – 68%. The in vitro release profile was best fitted to the Baker-Lonsdale model. Conclusions: The type and tensoactive’s concentration play an important role on morphology and stability. The results suggest that POH exhibit potential to be transposed to nanosystems helping develop.

Acknowledgments: CAPES, SETI Paraná.

ENCAPSULATION EFFICIENCY OF A HYDROPHOBIC DRUG CANDIDATE IN PLA NANOPARTICLES BY USING TWO METHODS OF PREPARATION

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Introduction: The methods of preparation of the nanoparticles influence the entrapment of the drug in the nanoparticles. The AMTAC-01 (spiro-acridine derivate) presents low bioavailability in biological mediums. The aim of this study was evaluating the encapsulation efficiency of AMTAC-01 in PLA nanoparticles (nanospheres and nanocapsules) front two methods: nanoprecipitation and emulsification solvent evaporation by simple emulsion (O/W). Methods: The nanospheres were obtained dissolving the Polymer and drug in dichloromethane, this organic solution was sonicated in an aqueous solution containing polyvinyl alcohol (PVA 2% p/v) in sonicator. The nanocapsules were obtained after injection of an organic solution containing the polymer, drug, caprylic capric triglycerides (Mygliol® 812) and soybean phospholipids (Lipoid®) in the aqueous solution containing poloxamer 188 (Pluronic F-68 ® 1% p/v). The encapsulation efficiency (EE%) was analyzed by the indirect method with quantification of the free drug fraction present in the supernatant. The thermal analysis of the system was performed with simultaneous measurements of Differential Scanning Calorimetry (DSC) and thermogravimetry (TG/DTG), with a heating rate of 10ºC / min, with a temperature range of 40 to 500ºC in an atmosphere of nitrogen gas flow rate of 100mL / min. Results and discussion: The nanocapsules and nanospheres presented EE of 50.1 % and 84.5%, respectively. The nanocapsules obtained less EE%, this fact may be related to an intermediate solubility of AMTAC 01 in acetone. However, the EE depends on physical and chemical properties of encapsulating polymers, solvent systems, polymer–drug interactions, and properties of the continuous phase. The thermal analysis of nanocapsulas curves containing AMTAC-01 showed a slight increase in the mass loss temperature (right shift) when compared to the mass loss curve of the nanocapsules without drug, this fact may be related to a greater thermal
stability of the drug trapped in the nanoparticles, thus requiring higher energy (temperature) for degradation to occur. White and drug-containing nanospheres showed similar results, however, with lower degradation temperatures. **Conclusion**: The methods of preparation were satisfactory for AMTAC-01 encapsulation with differences in the encapsulation efficiency. **Financial support**: CNPq universal (446274/2014). **Acknowledgments**: CAPES and CNPq.

**FORMULATION DESIGN AND CHARACTERIZATION OF LIPID NANOCARRIERS CONTAINING DOXORUBICIN FOR THE TREATMENT OF CANCER**

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Doxorubicin (DOX) is a widely used drug for the treatment of cancer. However, treatment with DOX causes serious toxicological effects. Therefore, the objective is to develop and characterize nanostructured lipid carriers (NLC-DOX) and solid lipid nanoparticles (NLS-DOX) that may promote increased specificity and low cardiotoxicity. Formulations were prepared by hot emulsification-sonication method and characterized as encapsulation efficiency (EE%), nanoparticles diameter, polydispersity index (PDI) and zeta potential (ZP). A two-factor three-level central composite design (CCD) was applied to statistically optimize the formulations using Design-Expert software. According to the CCD matrix generated by Design-Expert software, a total of 21 experiments, including two replicates at factorial and axial points and five replicated center points, for statistical assessment the pure error sum of squares were constructed. The p-value less than 0.05 was considered to be statistically significant. The factors studied (liquid lipid and co-sufactant concentrations at three levels) had a statistically significant influence on the EE (%) and particles diameter responses. The composition of optimal formulation was determined as 20% (w/w) liquid lipid and 1% (w/w) co-surfactant for 0.15% (w/w) of DOX in NLC. The results showed that the optimal formulation of NLC-DOX had EE% of 88.7%, particle size of 89.2 nm, ZP of -19.1 ± 1mV and PDI of 0.21. As perspective, stability studies and in vitro evaluation of cytotoxicity were required. **Financial Support and acknowledgements**: Capes, CNPq and Fapemig.

**EXPERIMENTAL DESIGN APPROACH TO DEVELOP NOVEL ANTIMALARIAL NANOEMULSIONS**

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Introduction: Malaria causes millions of deaths annually, being the oral medication required for its treatment. In this work, we have been developing nanoemulsions (NEs) containing a novel antimalarial drug by mean the experimental design approach. **Methods**: Oil-in-water NEs were developed by high pressure extrusion method. A 2³ full factorial design with five central point replicates was performed aiming at to evaluate the effects of amount of surfactant, agitation time and amount of oily phase in the droplet size (nm), polydispersion index (PDI) and drug incorporation of the NEs. **Results and discussion**: Nine different NEs were obtained. Most had droplet size smaller than 300 nm and PDI ≤ to 0.3, which indicate suitable physicochemical stability. On the other hand, all NEs presented drug incorporation greater than 96%. The studied factors significantly affected most of the NEs’s physicochemical properties at different levels (p < 0.05). The droplet size was affected by the interaction between the amounts of surfactant and oily phase. Concerning the PDI, only the amount of surfactant was significant. However, none of the studied factors significantly influenced the drug incorporation. **Conclusions**: Such experimental design was successfully applied in the development of novel antimalarial NEs, enabling the comprehension and control of factors affecting their stability. Our data open perspectives for further investigations regarding the in vitro performance of these NE as an advance in the treatment of neglected diseases like malaria. **Acknowledgments**: UFSJ, UFOP, FAPEMIG and CAPES.
THERMODYNAMIC INTERACTION BETWEEN TRANSMEMBRANE PH-GRADIENT LIPOSOMES WITH A DRUG MODEL BY ISOTHERMAL TITRATION CALORIMETRY

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Introduction: Transmembrane pH-gradient liposomes have been explored due to their promising drug-carrying ability. A better elucidation of the molecular mechanisms involving the interaction between the drug and these particles is an important aspect in the research and development of new formulations involving this technique. This work aimed at conducting a thermodynamic characterization of the binding process between lidocaine, used as model drug, and liposomes with transmembrane pH-gradient using isothermal titration calorimetry (ITC).

Methods: Various liposome compositions were compared, varying concentration of the lipids phosphatidylcholine (DSPC, DMPC, DPPC, EGGPC, HSPC), phosphatidylglycerol (DSPG), phosphatidylethanolamine (DMPE, DPPE), cholesterol and DSPE-PEG. Different hydration buffers with pH gradients (inner 3.0 and external: 7.4), sodium citrate, ammonium citrate and ammonium sulfate, were tested and compared by ITC at 37 °C.

Results and discussion: Thermodynamic analysis suggested that lipid composition and hydration buffer altered significantly the interaction processes, observed through the differences in the ITC profiles. Generally, the technique demonstrated favorable enthalpic and entropic contributions to the interactions. We observed that the bonds were predominantly enthalpic, resulting from the hydrophobic effect of the phospholipid membranes. Based on the results, the best drug-lipid interaction was observed between liposomes composed of cholesterol+DSPE-PEG+DSPC and the model drug, and using ammonium citrate (pH = 3.0) as the hydration buffer. Conclusion: ITC technique proved to be effective to clarify the binding profile between drug and pH-gradient liposomes, being an important technique for characterization and comparison between formulations and their ability to interact with drugs.

OPTIMIZATION OF SURFACANT TYPE AND AMOUNT FOR ENCAPSULATION OF VORICONAZOLE IN PCL NANOPARTICLES

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Introduction: Voriconazole (VCZ) is an antifungal triazole used in the treatment of aspergillosis, which low solubility in water makes it difficult for intravenous administration. Different studies focus on improving its bioavailability and decreasing adverse effects by the use of drug delivery systems, such as polymeric nanoparticles, to improve drug solubility. Objective: Evaluate the effect of surfactant concentration and the lipid concentration in the mean diameter and PdI of polymeric nanoparticles containing VCZ. Methods: Nanocapsules and nanospheres were prepared by the nanoprecipitation method, adding VCZ at 0.50 mg/mL. Mean diameter and size distribution were determined by Dynamic Light Scattering. Encapsulation efficiency was measured by HPLC after separation of the free drug by centrifugation. Results and discussion: Encapsulation efficiency varied from 34-88%, mean size from 124-225 nm and PdI from 0.038-0.2, depending on the amount of oil in the formulation, which varied from 2.50-100 mg. The combination of polysorbate 80 and sorbitan monooleate, together with lower lipid concentration, resulted in size decrease and higher VCZ encapsulation efficiency. Conclusion: This work presents a feasible formulation for preparing polymeric nanoparticles loaded with VCZ, and demonstrated how physical-chemical parameters of polymeric nanoparticles loaded with a lipophilic drug can be improved by the variation of the surfactant and by the amount of lipids, increasing the drug encapsulation efficiency.
REBUILDING THE DAMAGED MYOCARDIUM WITH EMERGING THERAPIES: STEM CELLS, BIOMATERIALS AND NANOPARTICLES

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Introduction: Cardiovascular diseases (CVD) are the leading cause of death worldwide. Novel therapeutic strategies under investigation include gene, cell, biomaterial and growth factor therapy. Methods: Our research team has focused efforts to develop synergistic approaches for cardiac repair. These include: (1) nanostructured systems for growth factor delivery; and (2) biomaterial scaffolds to carry stem cells. We developed poly (lactic-co-glycolic acid) (PLGA) nanoparticles containing adrenomedullin-2 (ADM-2). Results and discussion: High encapsulation efficiency was reached (ca.70%) for 300 nm-sized particles with zeta potential around – 30 mV. Electron microscopy analysis by SEM and TEM revealed spherical particles with a smooth surface. ADM-2 associated to nanoparticles was also determined by EDS elemental analysis, SDS-PAGE and LC-MS/MS for peptide identification. Importantly, encapsulated ADM-2 significantly induced cell proliferation in HUVEC and EA.hy926 endothelial cells, indicating preservation of ADM-2 bioactivity. Concerning to biomaterial strategy, we have developed a silk fibroin-based injectable hydrogel. FT-IR spectroscopy analysis confirmed the conformational change in the silk fibroin scaffolding structure. A 3D porous morphology was imaged by SEM, which confirmed the matrix scaffold architecture. This spatial pattern allowed attachment and viability of L929 fibroblasts and mesenchymal stem cells by confocal microscopy and Live/Dead cell viability assay, respectively. Conclusions: In summary, these findings demonstrate the feasibility of using PLGA nanoparticles as delivery systems for the angiogenic peptide ADM-2. In addition, silk fibroin hydrogel provided a versatile and biocompatible platform for cell delivery. Currently, association between these two approaches is being assayed in vitro as a previous step for in vivo evaluation in an animal model of myocardial ischemia.
Section
Pharmaceutical Services
FACTORS ASSOCIATED WITH HIGH MEDICATION REGIMEN COMPLEXITY IN ELDERLY PATIENTS

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Introduction: Complex medication regimens are common in elderly, favoring the occurrence of undesirable health outcomes. Therefore, it is important to understand the individual factors associated with complex regimens. Purpose: To investigate the factors associated with high regimen complexity in the elderly. Methods: Cross-sectional study with elderly patients (≥60 years) who received at least one medication in the pharmacies of two primary health care centers in southeastern Brazil. Data were collected through face-to-face interviews, using a structured questionnaire. Regimen complexity was measured using the Brazilian version of the Medication Regimen Complexity Index. The association between high regimen complexity (index>16.5) and independent variables was evaluated using binary logistic regression. The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE: 17339713.4.0000.5149). Results and discussion: 227 participants were included, with a mean age of 71.4 years and mostly females (70.9%). The median complexity index was 10.5 (3.0-16.5) and 20.8 (17.0-38.0) for low/mean and high complexity scores, respectively. High complexity scores were associated with diabetes (OR=5.4; p=0.00) and respiratory diseases (OR=3.0; p=0.02). Patients with these diseases use medications that are administered by non-oral routes and require special devices and additional instructions for administration, which can increase regimen complexity. Conclusions: Elderly with diabetes and respiratory disease were most likely to have complex regimens. Therefore, it is important to include such patients in pharmaceutical care services, which can contribute to reduce regimen complexity, avoid medications non-adherence and hospitalization.

Financial Support: Fundação de Amparo à Pesquisa do Estado de Minas Gerais.

ADVERSE DRUG REACTIONS USED FOR THE TREATMENT OF ALZHEIMER’S DISEASE: CROSS-SECTIONAL STUDY

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Introduction: Alzheimer’s disease is the most common type of dementia and is considered a worldwide public health problem due to the increasing increase in the elderly. National data related to the safety of drugs used for the treatment of Alzheimer’s disease are scarce. This study determined the prevalence of suspected adverse drug reactions used for the treatment of Alzheimer’s disease, provided by Specialized Component of Pharmaceutical Assistance of the Unified Health System. Methods: This is a cross-sectional and analytical study performed in Sorocaba, state of São Paulo, Brazil. The information was collected from the database MEDEX and interviews with patients and/or caregiver. Suspected adverse drug reactions were self-reported and categorized by physiological system, the frequency of occurrence and severity. The categorical variables were described by absolute and relative frequency and the quantitative variables by mean and standard deviation. Results and discussion: Of the 285 patients registered in the database for the withdrawal of drugs for the treatment of Alzheimer’s disease, data were collected from 250 them. The presence of at least one possible adverse drug reaction was observed in 209 (83.6%) patients. They were predominantly women, age group of 75 years or more and with diagnosis time of disease between two and 10 years. Donepezil and galantamine were the drugs most commonly used. There were 933 reports of adverse drug reactions and the donepezil was the drug with the highest number of people with adverse effect (41.6%). The adverse effects were associated mainly with the central nervous system; most of them were of common frequency (57.1%) and mild severity (89.0%). Conclusions: There were a high number of reports of adverse drug reactions, considered of common occurrence and mild severity. These results characterized the safety of the treatment of Alzheimer’s disease and contribute to guide prescribers and health managers in improving care related to drug treatment of this population.

Ethical approval: The study was approved by the Ethics and Research Committee of the University of Sorocaba (protocol number: 1,860,724).
ASSESSMENT OF THE THERAPEUTIC VALUE OF NEW BIOLOGICAL DRUGS MARKETED IN BRAZIL

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Introduction: Biologicals drugs represent an important and growing part of therapeutic arsenal. Purpose: To examine the therapeutic value of new biological drugs marketed in Brazil. Methods: Retrospective cohort study including new biological drugs registered between January 2003 and December 2017 in the National Health Surveillance Agency (Anvisa). The cohort was defined after identification of new drugs launched abroad in the period of research and also approved in Anvisa. In the database Drugs @ FDA Food and Drug Administration (FDA), the new drugs registered in the United States were identified and registered medicines in other countries were identified in review articles. The level of therapeutic innovation was determined using the Motola algorithm. Results and discussion: Of the 60 drugs in the cohort, 23 (38.3%) were first class and 08 (13.3%) orphan drugs. According to the Anatomical Therapeutical Chemical Code System first level, the most frequent groups were Antineoplastic and Immunomodulating Agents (50.0%), Digestive Tract and Metabolism (21.7%). In Motola Algorithm 19(31.7%) were rated as pharmacological or technological innovations and 41(68.3%) were rated as therapeutic innovations. Only 12(20.0%) were rated as important innovations. In line with studies in other countries small number of new drugs in Brazil are highly innovative. Innovative drugs should offer improvements over existing therapies and step changes in terms of outcomes for patients. Conclusions: Important therapeutic innovation drugs comprise only a fifth of all new biological drugs registered in Brazil. Financial support: Fundação de Amparo à Pesquisa do Estado de Minas Gerais.

ANÁLISIS DE MEDICAMENTOS PROVEDIDOS POR JUZGADO DE JUSTICIA EN LA REGIÓN NORTEOFENAL DEL ESTADO DE RIO GRANDE DO SUL

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Introduction: The demand for medicines through the judiciary process has been increasing gradually, because according to the Brazil law the right to health is considered fundamental to the citizen and must be guaranteed by State. Thus, there are expenses with drugs that are not always included in the SUS list. The objective of this study was to analyze the profile of new judicial requests for drugs by the 12th Regional Health Coordination, located in the northwest of Rio Grande do Sul state, Brazil. Method: Observational, retrospective and transversal study was performed. Data were collected in the AME-CPAF / SES / RS system and was evaluated the patient age, gender, CID, pharmaceutical dosage form and drug concentration, from July to December 2016. Drugs were classified according to the ATC and their presence in REMUME and in the basic, strategic or specialized components of Pharmaceutical Assistance lists. Results and discussion: The protocol of 137 patients was analyzed and a predominance of women (69.34%), from 61 to 80 years old (29.19%) was observed. The main drugs classes requested were for CNS and Cardiovascular treatment and Immunomodulatory Agents. Conclusion: Knowledge about drug lawsuits and pathologies that affect the population can provide data that allow guiding the management of Pharmaceutical Assistance and promoting effective actions and improvements in public health.
MANAGEMENT TRAINING FOR PHARMACISTS IN SUS: PROMOTING THE DEVELOPMENT OF MANAGEMENT COMPETENCIES

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Introduction: The implementation of pharmaceutical services is pointed out as one of the challenges for the consolidation of SUS. The performance of pharmacists in SUS has required the development of competencies related to management. The objective of this work is to analyze the perspective of actors involved in a specialization course in management for pharmacists who work in the SUS, on the development of management skills. Methods: The course was conducted between 2010 and 2016, totaling 2,500 graduates. Aimed to promote the development of skills in public service management. To understand the perspective of the actors, three workshops were held with 68 stakeholders using SWOT analysis. Results and discussion: The results were discussed in the categories: management training, e-learning in continuing education, course’s infrastructure, issues related to public health services working conditions, interprofessional work, and political and social sceneries in Brazil. The practical activity developed in the service (Operative Plan) was important for the development of competencies related to leadership, creativity, autonomy and commitment to the results of health policy. Difficulties in service such as lack of support from municipal management in carrying out qualification activities were identified as weakness in the learning process. Conclusions: The performance as manager demands skills sometimes not taught during professional training. In developing the Operative Plan, the pharmacist interacted with the other actors, promoting interdisciplinary and the exercise of managerial tools. Management training for health professionals needs to consider the promotion of contents and activities consistent with the services.

WHAT IS THE IMPACT OF CONTINUING EDUCATION FOR HEALTH PROFESSIONALS?

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Introduction: Continuing education (CE) processes after graduation are important and necessary because they involve the updating of knowledge and the improvement of professional practice, and may imply the maintenance of professional registration, as in some European countries. Due to the relevance of the theme, authors highlight the need to evaluate EC experiences, considering the processes, results and impact. The objective was to carry out a review of the scope of studies that evaluated the impact of continuing education on health. Methods: A review of the scope of the in the databases PUBMED, LILACS, SCOPUS and ERIC, revised in pairs, using terms related to the CE, the impact of the evaluation, and health professionals in Portuguese, English or Spanish. Results and discussion: The search indicated 1112 studies in SCOPUS, 693 in PUBMED, 330 in ERIC and 115 in LILACS, totaling 2250 studies. Of these, 248 articles were excluded (duplicated or because they did not meet the inclusion criteria for language) and 1970 after reading titles and abstracts. A total of 248 studies were selected for reading the whole, and articles that report a CE intervention lasting less than 20 hours, according to inclusion criteria, will still be excluded. Conclusion: The preliminary analysis points to a heterogeneity of the methods of evaluation of the impact of educational interventions in health. It is also relevant to note that most articles don’t cite the concept of the term impact used.
Introduction: Dyslipidemia is a metabolic disease characterized by elevated plasma LDL-C levels, reduced HDL-C levels and / or increased triglycerides, with a high risk of coronary events due to atherosclerosis. The study evaluated compliance with the Clinical Protocol and Therapeutic Guidelines (CPTD) - Dyslipidemia: prevention of cardiovascular events and pancreatitis and the perception of pharmacists and managers regarding the data. Methods: Retrospective observational study of the drug release processes for the treatment of dyslipidemia according to CPTD - Dyslipidemia in dispensing pharmacies of the specialized component of pharmaceutical service and qualitative analytical-descriptive guidance with pharmacists and system managers. Results and discussion: Of the 146 cases, 61.6% presented the inclusion criteria. Only in 19.4% the initial values of triglycerides were above 500mg / dL and in 72.3% the values were lower than recommended. No evidence of exclusion criteria was identified. However, in relation to hyperthyroidism, 2.1% presented TSH levels above 10mUI / mL and 7.5% with no hormone dosing data. Initial CPK and hepatic transaminases dosages were not present in 6.8% and 3.4% of the processes, respectively. For pharmacists and managers, noncompliance with the CPTD is due to insufficient training of professionals, insufficient human resources and to the faulty evaluation process by the Pharmacy and Therapeutics Commission. Conclusion: CPTD - dyslipidemia has not been effectively fulfilled and continuing education of professionals and management commitment should be priorities to ensure the safety and efficacy of treatment.

Ethical aspects: The work was previously approved by the Ethics and Research Committee on Human Beings of the Vila Velha University, (721.998/2014).

Acknowledgments: This research was supported by the Foundation for the Support of Research and Innovation of the Espírito Santo State (FAPES) and Coordination for the Enhancement of Higher Education Personnel (CAPES).

PHARMACEUTICAL SERVICE IN THE FIELD OF THE PUBLIC HEALTH SYSTEM: DISSATISFACTION OF USERS, MANAGERS AND PHARMACISTS

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Introduction: Pharmaceutical Service (PS) is characterized by actions aimed at access and rational use of medicines. The study evaluated the PS indicators of the public health system, the satisfaction and perception of the users and the impression of managers and pharmacists in relation to the verified data. Methods: Indicators of PS structure, process and outcome under the public health system were evaluated. The level of satisfaction of the users with the services of the pharmacies of this system were analyzed through semi-structured questionnaire and the perception of these users analyzed by the discourse technique of the collective subject. Using the focal group technique, the impression of managers and pharmacists was collected. Results and discussion: The data showed that in only 44.4% of the pharmacies the pharmacist was present in full time, which possibly hindered communication with users. Only 33.3% of the items for Good Drug Storage Practices were met, which could impair the quality of medicines. The level of satisfaction of the users was of 3.2±0.6, indicating dissatisfaction with the services of the pharmacies, which was reinforced when the users demonstrated the need for pharmaceutical guidelines to ensure satisfaction. For managers and pharmacists these results were related to inadequate physical structure of pharmacies, work overload, lack of interaction between the public health system team and lack of prioritization of PS by management. Conclusions: PS within the public health system has structural and organizational weaknesses that require changes and in general, users are dissatisfied with the services of public pharmacies, especially with the pharmaceutical care.

Ethical aspects: The work was previously approved by the Ethics and Research Committee on Human Beings of the Vila Velha University (1.920.600/2017).

Acknowledgments: This research was supported by the Foundation for the Support of Research and Innovation of the Espírito Santo State (FAPES) and the Coordination for the Enhancement of Higher Education Personnel (CAPES).
ADEQUACY OF THE PHARMACOTHERAPEUTIC FOLLOW-UP IN BRAZILIAN HOSPITALS ACCORDING TO THE INTERNATIONAL STANDARDS RECOMMENDED BY THE INTERNATIONAL PHARMACEUTICAL FEDERATION

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Introduction: Hospital pharmacotherapeutic follow-up is a service of great importance both for the quality and safety of the patients’ treatment, and for the hospital efficiency and reduction of the costs with treatment complications due to ineffectiveness, adverse effect or mistake. The objective of the present study was to analyze the adequacy of the Brazilian Hospital Pharmacy towards the pharmacotherapeutic follow-up. Methodology: A questionnaire developed following the 65 declarations of Basel created by the International Pharmaceutical Federation in 2015 was sent by email to hospital pharmacists from the whole country. The question analyzed in this study concerned the declaration number 8 which aims to analyze the pharmacotherapeutic follow-up in hospitals. All statistical analyzes were performed by IBM SPSS v.19. Results and discussion: A total of 111 pharmacists from hospitals of high and medium complexity from all Brazilian regions answered to the questionnaire. Only 68.5% (n=72) of these professionals declared to follow patients in use of medication aiming to provide safety, the proper use of medications and better therapeutic results for outpatient and hospitalized persons. Conclusion: The study showed that the pharmacotherapeutic follow-up in Brazil still needs to be introduced in more hospitals. It is important that pharmacists discover the relevance of this new role in their functions and show how indispensable it is through actions aiming to guarantee the access, rational use and safety of the prescribed medication.

Ethical approval: CAAE:56738416.3.0000.5545 - Fundação Universidade Federal de São João Del Rei - C. C. Oeste Dona Lindu.
Financial support: International Pharmaceutical Federation (FIP).

INFLUENCE OF POLYPHARMACY ON THE ADHESION TO ANTIRETROVIRAL THERAPY IN ADULTS AND ELDERS LIVING WITH HIV/AIDS

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Introduction: The advent of antiretroviral therapy has contributed to an increase in the life expectancy of people living with HIV / AIDS. Antiretroviral therapy is known to include combinations of three or more drugs of different therapeutic classes and that the aging of patients on antiretroviral therapy results in extensive use of drugs. Polypharmacy, in its turn, may hinder adherence and compromise treatment in people living with HIV / AIDS. Thus, the present study aims to evaluate the association between polypharmacy and non-adherence to antiretroviral therapy in adults and elders living with HIV / AIDS. Methodology: It is a cross-sectional study developed with 108 patients, 54 adults between 36 and 45 years of age and 54 elderly people between 60 and 68 years of age, attending the Specialized Care Service (SAE) in Divinópolis-MG. The odds ratios (OR) and their respective confidence intervals (95% CI) were calculated in order to verify the association between polypharmacy and nonadherence to antiretroviral therapy. Results and discussion: Polypharmacy was more present among the elders (51.90%), however, non-adherence to antiretroviral therapy was more observed among adults (46.30%). The results of the univariate analysis revealed that patients in polypharmacy had a lower chance of not adhering to antiretroviral therapy (OR = 0.301, 95% CI = 0.111-0.815). Conclusion: Contrary to the expectations, patients on concurrent use of many drugs adhered more to antiretroviral therapy. Ethical approval: CAAE:41775015.3.0000.5545 - Fundação Universidade Federal de São João Del Rei - C. C. Oeste Dona Lindu.
Financial support: CNPq.
EVALUATION OF THE ANTIMICROBIALS PRESCRIPTIONS DISPENSED AT THE BASIC PHARMACY MUNICIPAL DE CUITÉ/PB

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Introduction: Antimicrobials are substances of natural or synthetic origin that eliminate or inhibit the growth of microorganisms. The indiscriminate use of these drugs in the treatment of diseases has a great impact on public health, as it can lead to the dissemination of resistant microorganisms, causing loss of antimicrobial efficacy. The objective of this study was to evaluate the prescriptions regarding the cause of the indication and main antimicrobials prescribed, as well as the prescribers of these medicines, dispensed at the Basic Pharmacy Municipal of the city of Cuité-PB, besides verifying the adequacy of the recipe to the current legislation (RDC nº 20/2011 - ANVISA). Method: A cross-sectional, qualitative-quantitative and descriptive study was conducted with data collected between October and November 2017, from the application of questionnaires. The research was approved by the Ethics Committee (nº 2,065,111). Results and discussion: 120 users were evaluated. The main reports were pharyngitis and vaginal infection. The most commonly used antimicrobials were cephalexin (32.5%) and metronidazole (23.6%), prescribed mainly by a general practitioner (79.2%) and a geriatrician (10.2%). It was also reported that those did not provide medication information (45.9%) and most users did not seek medical follow-up (65.0%). With respect to recipe, 26.7% presented a disagreement mainly due to the absence of treatment time (88.6%). Conclusion: Therefore a need for pharmaceutical guidance next to users and sensitization of prescribers for the rational use of drugs in order to minimize health problems related to the loss of efficacy of antimicrobials due to bacterial resistance.

RELATIONSHIP ON JOB SATISFACTION, DEPRESSION, BURNOUT SYNDROME AND THE PATIENT SAFETY CULTURE: CROSS-SECTIONAL STUDY WITH STRUCTURAL EQUATION MODELLING ANALYSIS

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Introduction: Evidence is needed to support the theory that psychosocial factors reflect on the safety of care provided in health services. The aim of this study is to evaluate if patient safety culture is related to job satisfaction, depression and burnout syndrome among professionals in the hospital setting. Methods: This is a cross-sectional study conducted between August and November 2016 in a reference teaching hospital for 13 cities in State of São Paulo. Professionals were recruited through random probabilistic sampling. Data were collected through psychometric instruments to analyze job satisfaction (Job Satisfaction Survey-JSS), the presence of depression (Patient Health Questionnaire-9), and burnout syndrome (Maslach Burnout Inventory–MBI), as well as the relationship between these factors with patient safety culture (Safety Attitudes Questionnaire–SAQ). The prevalence ratio (PR) was calculated using a Poisson regression. The partial least squares structural equation modeling (PLS-SEM) was used for analysis. Results: 271 professionals participated in this study. Subjects with a professional activity time between 11-20 years showed a more negative perception of the safety culture when compared to those with less than one year in the job (p=0.05). Technical support workers of the hospital revealed higher levels of job satisfaction than health professionals (p=0.02). Subjects classified in D-E socioeconomic level (lower average domestic income) showed twice the prevalence of depression compared to those in class A (PR=2.84, 95%CI:1.24-6.51, p=0.01). Men showed burnout approximately twice as much as in women (PR=1.98, 95%CI:1.03-3.79, p=0.04). PLS-SEM confirmed the relationship of job satisfaction and the absence of burnout syndrome as predictive aspects of the patient safety culture (p<0.001). Discussion: Differently from the existing scientific evidence, this study presents detail and focus on different areas and professional categories present in a hospital. These findings suggest that psychosocial factors influence the quality and safety of care provided by health workers. Conclusion: The perception of patient safety culture is related to job satisfaction and burnout syndrome in hospital professionals. Ethics approval: The research was approved by the Research Ethics Committee of the State University of São Paulo (Protocol no. 1.644.886). Financial support: National Council for Scientific and Technological Development – CNPq (Grant: 130828/2016-5).
PHARMACOTHERAPEUTIC FOLLOW-UP OF OUTPATIENTS WITH RHEUMATOID ARTHRITIS IN TEACHING HOSPITAL: PILOT STUDY

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Introduction: The pharmacist can contribute to the evaluation of the effectiveness and safety of rheumatoid arthritis (RA) treatment, with interventions that improve adherence to treatment, acting collaboratively with other professional practices. Thus, this work was developed by the Pharmacy Department in partnership with the University Hospital’s Ambulatory Pharmacy (UH), with the aim of implementing a Pharmaceutical Care Unit. Method: Descriptive and longitudinal research which concluded pilot study related to pharmacotherapeutic follow-up (PF). An initial phase of awareness among the professionals involved (physicians, nurses and pharmacists) was carried out. After approval by Ethics Committee of the UH (Approval number 1.834.713), PF occurred in 2 consultations, with interval of 3 months, using the Dáder method. Results and discussion: The acceptance rate for PF after the service offer uptake was 55.6% (n = 20), 75% of which were referenced by the Pharmacy (dispensing area). Thus, strategies to improve team awareness (doctors and nurses) are necessary, especially regarding patient referrals. The patient’s rate with drug-related problems (DRP) was 85% and 59 DRPs were detected, of which 32.2% were considered real problems. Of these, 67.8% were resolved, with 40% related to effectiveness and 20% to safety. Interventions were suggested (n=124), of which 91.1% were accepted by the patients. In addition, some interventions were suggested to physicians (n=11), which 45.5% were performed. Conclusion: In view of the DRP observed and the rate of acceptance in participating in PF, the importance of pharmaceutical performance in the optimization of pharmacotherapy was evidenced. (Support: CAPES, CNPq)

IMPROVING THE CARE OF DEINSTITUCIONALIZED PEOPLE WITH SEVERE MENTAL ILLNESS: EVIDENCE SYNTHESIS

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Introduction Considering the complexity of the care of deinstitutionalized people with severe mental illness (SMI) and the context of one of the largest Brazilian asylum centers, the objective of this study was to subsidize actions and strategies to improve the care of people with SMI in the region of Sorocaba, belonging to the Regional Health Department - 16 (DRS-16) based on the best available scientific evidence. Methods: We identified systematic reviews focusing any type of care strategies for deinstitutionalized people with SMI, and treated in the community published up to 16 March 2018 in Cochrane Library; Epistemonikos, PubMed, Health System Evidence, Rx for Change; Health Evidence, CINAHL, EMBASE, PSYCINFO and LILACS without any restrictions in terms of language and status of publication. A team of reviewers independently assessed titles, abstracts, and completed text to determine eligibility. For eligible studies, the same reviewers performed data extraction and evaluated the risk of bias and quality of selected systematic review using AMSTAR tool. The primary outcomes were: hospitalization, compliance, global state improvements, social functioning and satisfaction. Results and discussion: ten systematic reviews met the inclusion criteria. The strategies that were most likely to have a positive impact included: Intensive Case Management, Community mental health teams, Psychoeducation, psychiatric hospital Day, Therapeutic Residential Services. These five strategies should be acting in an integrated and organized manner to obtain positive outcomes. Conclusion: most of these strategies are described in the Brazilian Policy, but exists some barriers to overcome. What is needed now are adjustments to promote the effective implementation in the DRS-16. In turn, must be carefully evaluated, including monitoring patients and healthcare team.
SAFETY ASSESSMENT BETWEEN MATRIX TECHNOLOGY COMPARED WITH MESALAZINE COATED TABLETS FOR ULCERATIVE COLITIS

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Introduction: Ulcerative colitis is a chronic disease characterized by inflammatory reactions in the colon. The administration of Multi Matrix Mesalazine (MMX®) can be used as treatment due to its high dose (1200 mg) and gradual release. Thus, this study aimed at gathering evidence on the safety of MMX® technology to be compared with conventional therapy (coated tablets of 800 mg), based on kind and frequency of side effects. Methods: Eligible studies were selected from Medline, Embase, Science Direct, Scopus and Clinical Trials databases, including prospective, randomized and double-blind studies that compared adverse effects that occur in two different groups: one using MMX® tablets and the other using conventional ones. The keywords were “MMX mesalamine”, “MMX mesalazine”, “MMX 5-aminosalicylic”, “MMX 5-ASA”, “multi matrix mesalazine”, “multi matrix mesalamine”, “multi matrix 5 -ASA”, “Ulcerative colitis”, “UC” and “side effects”, which were combined with the Boolean terms “or” and “and”. Results and discussion: Three papers were included: those developed by Kamm and collaborators (2007), Prantera et al. (2009) and D’Haens et al. (2012). Ulcerative colitis relapse and headaches were the most common adverse events and none of them was dose-dependent. In addition, the frequency of adverse effects and subjects rate affected were homogeneous between both groups. This result is congruent with other studies that analyzed the frequency and occurrence of side effects. Conclusion: These results suggest that the profile of unexpected reactions is inherent to mesalazine, but not due to pharmaceutical form or dose.

COMPARATIVE STUDY OF THE USE OF MMX AND CONVENTIONAL MESALAZINE TECHNOLOGY FOR THE CLINICAL AND ENDOSCOPIC REMISSION OF ULCERATIVE COLITIS

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Introduction: Ulcerative colitis is a chronic disease characterized by inflammatory reactions in the colon. Multi Matrix Mesalazine (MMX®) has been used as treatment due to its high concentration (1200 mg) and gradual release. Thus, this study aimed at gathering evidence of clinical and endoscopic remission rates of MMX® compared to conventional coated tablets (800 mg). Methods: A systematic review was carried out by selecting evidence from Medline, Embase, Science Direct, Scopus and Clinical Trials databases including prospective, randomized and double-blind studies to be compared with clinical and endoscopic remission rates shown in two different groups: one using MMX® tablets and the other using conventional ones. The keywords were “MMX mesalamine”, “MMX mesalazine”, “MMX 5-aminosalicylic”, “MMX 5-ASA”, “multi matrix mesalazine”, “multi matrix mesalamine”, “multi matrix 5 -ASA”, “Ulcerative colitis”, “UC” and “side effects”. The words were combined with the Boolean terms “OR” and “AND”. Results and discussion: Three papers were included: those developed by Kamm and collaborators (2007), Prantera et al. (2009) and D’Haens et al. (2012). Endoscopic remission rates were similar with both forms of the drug, showing no statistical difference. In terms of clinical remission, satisfactory results were reached, but with no statistical difference between conventional form and multi matrix technology. Conclusion: In spite of differences between technologies, both MMX® and coated tablets of mesalazine are capable of achieving good clinical and endoscopic remissions in patients with ulcerative colitis, allowing different kinds of therapy and more options for the treatment.
NEW DRUGS REGISTERED IN BRAZIL FROM 2003 TO 2013: ANALYSIS FROM THE PERSPECTIVE OF OLDER PEOPLE

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Introduction: Older People have been excluded from clinical trials conducted as part of the clinical development program of new drugs for ethical, methodological and practical reasons. Purpose: To analyze the new drugs from the older people perspective and investigate the availability of information relevant to appropriate prescribing in the package inserts. Methods: Retrospective cohort study including new drugs registered between 2003 and 2013 in the National Health Surveillance Agency (Anvisa). The cohort was defined after identification of new drugs registered abroad in the period of research and also approved in Anvisa. In the database Drugs @ FDA were identified the new drugs registered in the United States and in other countries were identified in review articles. The level of therapeutic innovation was determined using the Motola algorithm. Indication for conditions of geriatric interest and inclusion of information about safety and effectiveness were also identified. Results and discussion: In the study 128 drugs were included. The drugs with indication for conditions of priority interest in geriatrics were 11 (8.6%). The number of geriatric information included after registration was 34, which 26 (20.3%) were safety related. The most frequent therapeutic class was antineoplastic and immunomodulators (31.2%). Regarding the degree of therapeutic innovation, only 24 (18.8%) corresponded to important innovation. The package inserts present information without clarity and precision about doses and pharmacotherapeutic specificities of older people. Conclusion: New drugs registered did not present important therapeutic innovations and the number of drugs to treat conditions of priority interest in geriatrics was small.

CONSUMER PERSPECTIVES OF THE ADVANTAGES AND DISADVANTAGES OF USING SOCIAL MEDIA FOR HEALTH-RELATED PURPOSES

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Introduction: Social media (SM) is increasingly being used by consumers for health-related purposes, including interactions with peers about their health conditions and treatment options. This study explored consumers’ perceptions of the advantages and disadvantages of using SM for health-related purposes. Methods: Five focus groups comprising of thirty-six Australian adults with a chronic condition and on medication were conducted. Discussions were audio-recorded, transcribed verbatim, and thematically analysed. This study (project number 2015/895) received approval from the University of Sydney Human Research Ethics Committee. Results: Consumers reported several benefits of using SM for health stating that it was very convenient to access health-related information and for peer engagement; it was user-friendly and assisted in improving their health knowledge. It also empowered them and provided social and emotional support. The disadvantages included information overload, wasting time; negative feelings from the information obtained; doubts about online information credibility; and issues related to online interactions with peers. Conclusion: Despite some disadvantages reported, health-related use of SM led consumers to feel supported, knowledgeable, and empowered. Consumers’ motivation to continue accessing SM for health-related purposes opens up avenues for the delivery of services via social media.
BARRIERS IN PRIMARY HEALTH CARE FOR NOTIFYING MEDICATION RELATED ADVERSE EVENTS

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This study described how health professional recognize the notification of medication-related adverse events in Primary Health Care. This was a study with application of a semi-structured questionnaire in two stages: first applied with presence of interviewees in 24 health units; second application, to pharmacists on line. There were 230 respondents: 53 community health agents, 7 oral health agents, 25 nurses, 55 pharmacists, 18 doctors, 14 dentists, 58 nursing technicians. Of these 48.7% had university education and 51.3% technical level education. As barriers to notification, 36.1% of the responses cited the lack of efficacy in notification, and lack of standardization of notification was cited in 72.2% of the responses. The incapability of recognizing errors related to medications was cited in 50% of the responses. The fear of exposure in notifying and loss of professional reputation predominated as barriers to notification in the different groups. The authors observed that 51.7% of the respondents had no knowledge of the concept of Patient Safety. The barriers identified signal the need for interventions in the culture of patient safety.

MEDICINES DISPENSED IN PRIMARY HEALTH CARE CENTERS IN A CITY OF SOURHER BRASIL IN 2016

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Introduction: Drug utilization research is long established in primary care as a mechanism by which to measure and give a feedback on quality of prescribing and drug utilization. This study analyzed the medicines dispensed in primary health care centers pharmacies of Florianópolis/SC, Brazil. Methods: It’s a, cross-sectional retrospective study, developed through the analysis of drug dispensing registry database (January - December of 2016) of primary health care centers pharmacies in Florianópolis. The medicines were classified using the Anatomical Therapeutic Chemical Classification System (ATC). Eventually dispensing drugs were considered if dispensed up to 6 times a year. Continuous dispensing drugs if dispensed more than 6 times a year. Results and discussion: From January to December of 2016. A total of 817,082 medicines were dispensed to 207,190 users (58.2% woman; 41.8% men). Users between 31 to 59 years old (39%) were most prevalent. Medications that act in the Nervous and Cardiovascular system and antibiotics for systemic use were most dispensed. The more prevalent medicines dispensed were: acetaminophen, dipyrone, ibuprofen, nimesulide and omeprazole. Most of medicines were dispensed eventually (88.2%). During the period studied, the primary health care service of Florianopolis was responsible to provide medicines to approximately 50% of its population. The profile of the users attended is in line with that reported in national studies. Conclusions: The prevalence of medicine dispensed can be useful to infer and follow the patterns of drugs prescription in primary health care centers and allow the reflection of the possible use by the users.
NETWORK META-ANALYSIS OF LEUKOPENIA AND INFECTION ASSOCIATED WITH TYROSINE KINASE INHIBITORS FOR CHRONIC MYELOID LEUKEMIA

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Introduction: Tyrosine kinase inhibitors (TKIs) are the treatment of choice for chronic myeloid leukemia (CML). However, hematological serious grade 3-4 adverse events such as leukopenia are reported for this class. Besides, leukopenia can increase host susceptibility to infections. We aimed to compare the safety profile of the TKIs bosutinib, dasatinib, imatinib, nilotinib, ponatinib and radotinib. Methods: A systematic review with network meta-analysis (NMA) of randomized controlled trials (RCTs) was performed. Electronic searches were conducted in Pubmed, Scopus, Web of Science and Scielo. Bayesian NMA was performed considering the incidence of leukopenia and infections (ADDIS 1.16.8). Surface under the cumulative ranking curve analyses (SUCRA) were calculated based on the rank orders. Results and discussion: Eighteen RCTs were included in the NMA. For leukopenia, dasatinib (100 and 140 mg), and imatinib (400 and 800 mg) were less safer options than nilotinib (600 and 800 mg) odds ratio (OR) ranging from 0.10 with 95% CrI [0.02-0.62] to OR 0.38 with 95% CrI [0.16-0.88]). Although no significant differences between TKIs were observed for the incidence of infections, SUCRA demonstrated that dasatinib (140 mg and 100 mg) presented the highest probabilities to cause this outcome (around 45%). The worst safety profile of dasatinib for both outcomes may be due to its mechanism of action. Dasatinib binds to a high number of key-kinase targets of the immune system, including Lck, Lyn, Btk and Src. Conclusion: Dasatinib has greater immunosuppressive activity than the other TKIs, which should be considered by healthcare professionals when selecting patient’s therapy.

PSYCOTROPIC DRUGS DISPENSED IN PRIMARY HEALTH CARE CENTERS IN A CITY OF SOUTHERN BRAZIL

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Introduction: Psychotropic drugs, used in the treatment of mental health conditions and pain are among the most commonly used drug classes worldwide. Prescribing of these drugs is widespread in all health care settings, but the largest use occurs in primary practice. The health consequences of the prescription drug abuse are a problem that deserves attention. This study analyzed the prevalence of psychotropic drugs (PD) dispensed in pharmacies of the primary health care centers PPHCC in Florianopolis/SC, Brazil. Methods: It’s a retrospective cross-sectional study that used a secondary database containing the registry of medicines dispensed in the pharmacies of the PPHCC (January - December 2016). PD were classified according to the Anatomical Therapeutic Chemical Classification System (ATC) levels 2 and 5. Results and discussion: During the period studied, 47,412 PD were dispensed to 207,190 PHCC users (64.2% woman; 35.8% men), by which most were between 31 to 59 years old (55.3%). Its stands the important prevalence among elderly. Psychoanalytics drugs were the most dispensed (51.9%), followed by psycholeptics (30.2%) and antiepileptics (12.8%). The most prevalent PD dispensed were fluoxetine (19.7%), diazepam (16.2%), sertraline (15.3%) and amitriptyline (13.7%). Older adults and women are particularly vulnerable to PD abuse and non-medical use of medications. Older people tend to use several medications, they are more susceptible to accidental misuse or abuse. Conclusions: The results bring a perspective on PD prescribing and utilization providing information for implementation actions and strategies of the safe and rational use of medicines.
PROCESS OF IMPLANTING A PHARMACIST’S OFFICE IN BASIC HEALTH CARE: EXPERIENCE REPORT

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Introduction: Pharmaceutical care has been implanted in several scenarios over the last decades. This study aim to describe the implantation of a pharmacist’s office in the health basic care of a medium-sized municipality in southern Minas Gerais, Brazil.

Methods: This is an experience report based on semi-structured interviews conducted with actors involved in the process. The interviews were conducted nine months after the beginning of the implementation (November 2017) to favor the identification of challenges and potentialities. Results and discussion: The implantation began with a partnership between the Pharmacy course of a federal university and the Municipal Health Department (MHD). Following, a literature review was performed to verify successful implantation experiences. The MHD offered physical space in a basic health unit to perform care and the university prepared all the material that would be used in the consultations. Pharmacy students were trained to perform the consultations under the direct supervision of professors with experience in Clinical Pharmacy. The activity was linked as a curricular internship. The lack of pharmacists in the public network to collaborate in the consultations and financial resources to acquire materials to verify clinical parameters were pointed out as the main challenges of the implantation process. Nevertheless, there is a strong potential to achieve clinical, humanistic and economic results that justify the practice in primary care. Conclusion: The teaching-service integration and the basis in the literature were fundamental to the process. Service potential overcomes challenges and serve as an incentive for the pharmacist’s involvement in patient care.

Acknowledgments: Municipal Health Department of Alfenas-MG and NAFAU Team (Nucleus of Pharmaceutical Attention of UNIFAL-MG)

PROFILE OF COMPARATIVE COST-ANALYSES IN ACROMEGALY: A SYSTEMATIC REVIEW

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Introduction: Acromegaly is a rare disease that results in the enlargement of body extremities and in organomegaly. Treatments include surgery, drugs, and radiotherapy, which are all onerous. Therefore, well-conducted cost-analyses are crucial in the decision-making process. Methods: A systematic review of comparative cost-analyses studies on acromegaly therapies was performed following PRISMA and Cochrane recommendations. The search for records was conducted in PubMed, Scopus, and Web of Science (May 2018). The quality of the included studies was assessed using the Joanna Briggs Institute Tool. Results and discussion: From initial 547 records, 16 studies were deemed comparative cost-analyses and included in the review. Six were conference abstracts and 10 were journal articles. The studies could present more than one economic evaluation, and encompassed cost-effectiveness (n=13), cost-utility (n=5), and cost-consequence (n=1) analyses. All studies were model-based and evaluated only direct medical costs. Eleven records did not mention discounting and only 10 performed sensitivity analyses. The evaluations were divided into three groups: primary surgery versus preoperative pharmacological therapy, comparison between first-line pharmacological treatments, and comparison between second-line pharmacological treatments. Half of the studies were sponsored by pharmaceutical industries. Conclusions: Comparative cost studies on acromegaly have been performed in several scenarios, evaluating different phases of treatment. However, the studies present limitations and, overall, were considered of moderate quality.
Section
Pharmacology and Toxicology
STRUCTURAL ELUCIDATION AND EVALUATION OF ANTINOCICEPTIVE POTENTIAL OF A NEW N-ACYLHYDRAZONE DERIVATIVE

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The functionality of N-acylhydrazone has been reported as the pharmacophore group with a wide variety of biological properties, among them analgesic and anti-inflammatory activities. Thus, the objective of this study was elucidate structurally and evaluate the analgesic potential of a new N-acylhydrazone derivative (JR19). The compound previously synthesized was physicochemically characterized and the structural elucidation was performed by \(^1\)H and \(^{13}\)C NMR technique. In the pharmacological tests of formalin-induced nociception, orofacial pain and safety, Swiss adult mice of both sex were used. The results were analyzed by analysis of one-way variance and the protocols approved by the Ethics Committee on the Use of Animals of the Center for Higher Education and Development (n° 5905022016). The compound showed Log\(^\text{P}\) and \(^{13}\)C NMR DEPT-Q spectra showed chemical shift signals characteristic of the \(N’\)-[(1-H-indol-3-yl)methylene]-2-cyanoacetohydrazide structure. In the nociception and formalin-induced orofacial pain models, the 10 mg.kg\(^{-1}\) dose of the compound was active only in the second phase, promoting a significant reduction in the reactivity time of 93 and 70% respectively, suggesting to be devoid of central analgesic effect and possibly anti-inflammatory action retainer. In the evaluation of acute toxicity there was no death, no behavioral or physiological changes, indicating low toxicity of the molecule tested. These results indicate the effectiveness of the N-acylhydrazone derivative as an analgesic and anti-inflammatory, favoring the prospects for its future use with these therapeutic goals. Support: CNPq and UEPB.

ID: 14

ANTIFUNGALS INHIBIT MONOMICROBIAL AND MIXED BIOFILMS OF CANDIDA ALBICANS AND PSEUDOMONAS AERUGINOSA OR STAPHYLOCOCCUS AUREUS

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The interaction of Staphylococcus aureus and Pseudomonas aeruginosa with Candida albicans are frequent forming biofilms in medical devices. These co-infections have reflected higher mortality rates in nosocomial infections when compared to those caused by a single microbial species. The objective of this work is to evaluate the effect of micafungin (MCF) and amphotericein B (AMB) on mixed biofilms C. albicans/P. aeruginosa and C. albicans/S. aureus. Biofilms 24h pre-formed using 1 x 10⁷ CFU/mL for C. albicans (SC5314) and 1 x 10⁸ CFU/mL for S. aureus (ATCC 6538) and P. aeruginosa (strain 151) were treated with several concentrations of MCF or AMB in RPMI 1640 medium buffered with MOPS 0.16M at 35°C for 24h under 150 r.p.m. In parallel, monomicrobial biofilms were also treated. Biofilm biomass was quantified by the violet crystal staining and the minimum inhibitory concentration that inhibits 50% of the biofilm (BMIC\(_{50}\)) was determined. The BMIC\(_{50}\) obtained for the C. albicans/P. aeruginosa mixed biofilm was 16 μg/mL for MCF and AMB; on the other hand, these antifungal agents did not inhibit the C. albicans/S. aureus mixed biofilms at the tested concentrations (≤256μg/mL). Monomicrobial biofilms of C. albicans were inhibited by AMB (BMIC\(_{50}\)=8 μg/mL) and MCF (BMIC\(_{50}\)=16 μg/mL); and only monomicrobial biofilms of P. aeruginosa were inhibited by these antifungals (BMIC\(_{50}\)=32μg/mL for AMB and BMIC\(_{50}\)=128μg/mL for MCF). Thus, these data show the potential use of AMB or MCF in combating monomicrobial or mixed infections caused by C. albicans with P. aeruginosa or S. aureus.

ID: 26
SUSCEPTIBILITY OF MIXED BIOFILMS OF *Aspergillus Fumigatus* AND *Pseudomonas Aeruginosa* TO ANTIMICROBIALS

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Introduction: Mixed biofilms of *Aspergillus fumigatus* and *Pseudomonas aeruginosa* is frequent in chronic pulmonary diseases such as cystic fibrosis; and this lifestyle is related to the higher tolerance to the immune system and antimicrobials. The aim of this work is to evaluate the effect of antimicrobials on the mixed biofilm formation of *A. fumigatus* and *P. aeruginosa*. 

Methods: For mixed biofilm formation, 24h-biofilms of *A. fumigatus* (ATCC 16913) were interacted with *P. aeruginosa* (strain 151) into the 96-well microtiter plate in RPMI 1640 medium buffered with MOPS 0,16M. After 1.5 h at 35°C, the biofilms were treated with several concentrations of micafungin (MCF), caspofungin (CPF), amphotericin B (AMB) and polymyxin B (PMB). In parallel, monomicrobial biofilms were also treated. After 24 h of incubation at 35 °C the total biomass of biofilms were quantified by the violet crystal staining for determination of minimum concentration that inhibit 50% of biofilm (BMIC$_{50}$). 

Results and discussion: AMB B had a great impact on the *A. fumigatus* biofilms and also on the mixed biofilm (BMIC$_{50}$ ≤ 16 μg/mL). For *P. aeruginosa* biofilm, only PMB was effective to inhibit (BMIC$_{50}$ ≤ 16 μg/ml). However, the echinocandins MCF and CPF were effective only for mixed biofilm presenting BMIC$_{50}$s of 128 μg/mL and 256 μg/mL, respectively. 

Conclusion: AMB and the echinocandins were able to control the mixed biofilms of *A. fumigatus* and *P. aeruginosa*; and they may be a promising alternative for treatment of mixed biofilms. However, further studies to evaluate the antimicrobials in inhibiting the biofilms should be conducted. 

BRAZILIAN JOURNAL OF PHARMACEUTICAL SCIENCES
vol. 54, suppl. 2, 2018

TOBRAMYCIN PLASMA AND TISSUE PHARMACOKINETICS IN ACUTE AND CHRONICALLY BIOFILM FORMING Pseudomonas aeruginosa INFECTED RATS

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Introduction: Biofilms reduce tobramycin (TOB) bactericidal activity in vitro. The aim of this study was to evaluate the impact of acute and chronic biofilm-forming P. aeruginosa infection on TOB’s lung penetration. Methods: Protocols approved by CEUA/UFRGS (#32345). For chronic pneumonia, six weeks-old male Wistar rats were intratracheally inoculated with a suspension of alginate beads of P. aeruginosa ATCC® 27853 (10^7 CFU/mL). Blank beads groups received alginate beads without bacteria. Acute infection was produced by P. aeruginosa PA14 intratracheally inoculated (10^9 CFU/mL). Seven (acute) and 14 (chronic) days after infection TOB pharmacokinetics (PK) was determined in anesthetized rats following 10 mg/kg i.v. bolus dose. Blood and lung microdialysate (CMA/20 probe) samples were collected up to 12 h post-dose. Samples were quantified by LC-MS/MS. Non-compartmental analysis performed by Phoenix®. Results and discussion: Acute infection did not change TOB plasma disposition. A significant decrease in area under the curve (from 128 ± 19 to 31 ± 25 μg·h/mL), increase in clearance (from 0.07 ± 0.01 to 0.61 ± 0.33 L/h/kg) and in volume of distribution (from 0.49 ± 0.1 to 0.74 ± 0.56 L/h) was observed in chronically infected animals. Alginate beads did not interfere with TOB plasma disposition. TOB lung exposition was reduced in approximately 73% in chronically and acutely infected animals (from 105 ± 12 to 26 ± 13 and 32 ± 17 μg·h/mL, respectively). Similar reduction in lung exposition was observed in blank beads group. Conclusion: TOB lung disposition is reduced in acute and chronic biofilm forming P. aeruginosa infections.

Development institution: Pharmaceutical Sciences Graduate Program, Federal University of Rio Grande do Sul.

EFFECTS OF HYDROQUINONE EXPOSURE ON THE CELLULAR AND HUMORAL RESPONSES INDUCED BY IMMUNIZATION AGAINST INFLUENZA VIRUS

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Introduction: Influenza virus infection is a health problem worldwide capable of causing severe complications. Vaccination is the best way to protect against Influenza. Evidence has supported that active immunization is impaired by exposure to some environmental pollutants, including cigarette smoke. We have shown that hydroquinone (HQ) is a contaminant of matter particle in tobacco and leads to several toxic effects on immune system. AIMS: To investigate the effects of in vivo HQ exposure on adaptive immunity induced by influenza vaccine. Methodology: Male C57BL/6 mice were daily exposed to nebulized HQ (2500 ppm) or PBS for 8 weeks (1h/day). At weeks 6 and 8, mice were immunized with the influenza vaccine. Samples were collected at weeks 6 and 8 during HQ exposure and 7, 35 and 70 days after the vaccine booster. CEUA/FCF protocol 506. Results/discussion: HQ slightly reduced some erythrocytic parameters and did not alter body weight and biochemical markers of liver and kidney functions, suggesting no apparent toxicity. Moreover, HQ exposed-animals presented altered morphology of spleen follicles and increased lymph nodes, with a reduction of specific IgG-secreting cells though. Avidity and titers of antigen-specific IgG were not altered, although IgG2c titers of HQ exposed-animals were reduced after the booster, suggesting a less sustained humoral response. Finally, HQ exposure increased the oxidative stress in splenocytes, suggesting a mechanism of HQ toxicity. Conclusions: Our data point out for novel target tissues of HQ toxicity. Even though chronic HQ exposure caused no apparent toxicity, it probably enhances susceptibility to Influenza virus infection.
HIPPOCAMPAL EXPOSURES OF QUETIAPINE FOLLOWING LIPID CORE NANOCAPSELS DOSING TO MALE AND FEMALE SCHIZOPHRENIA-PHENOTYPED WISTAR RATS

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Introduction: Antipsychotic treatment variability can be due to impaired drug brain penetration. We aim to compare quetiapine (QTP) delivery by lipid core nanocapsules (QLNC) and QTP solution (FQ) to hippocampus of male and female schizophrenia-phenotyped rats (SPR). Methods: Study approved by CEUA/UFRGS (#31001). QLNC (1 mg/mL) were obtained by nanoprecipitation. Wistar pregnant dams (GD15) received a single 4 mg/kg i.v. bolus dose of poly(i.c). SPR adult offspring (PND75) were divided in four groups: male and female FQ and QLNC (n = 6-8/group). Microdialysis probes (CMA 12, 3 mm) implanted in the hippocampal were used to access unbound QTP concentrations; jugular vein was cannulated for blood sampling. Pharmacokinetics (PK) was evaluated after QTP i.v. dosing as FQ (10 mg/kg) or QLNC (5 mg/kg). PK parameters determined by Phoenix® v. 6.4. Results: Significant reduction in CL<sub>Ltot</sub> (L/h/kg) was observed for QLNC groups (QLNC<sub>male</sub>: 0.64 ± 0.24; QLNC<sub>female</sub>: 0.58 ± 0.10; FQ<sub>male</sub>: 1.42 ± 0.42; FQ<sub>female</sub>: 1.47 ± 0.45) (p < 0.05), leading to increased AUC<sub>Ltot</sub>/D (QLNC<sub>male</sub>: 1237 ± 387; QLNC<sub>female</sub>: 1181 ± 154; FQ<sub>male</sub>: 740 ± 140; FQ<sub>female</sub>: 730 ± 188) (p < 0.05). Significant increase in hippocampal exposure (AUC/D) was observed (QLNC<sub>male</sub>: 229 ± 49; QLNC<sub>female</sub>: 228 ± 40; FQ<sub>male</sub>: 108 ± 31; FQ<sub>female</sub>: 112 ± 17) (p < 0.05). No differences were found in plasma or hippocampal parameters between male and female SPR compared within the same formulation. Conclusions: QTP hippocampal exposure is reduced in SPR in both sexes. Drug nanoencapsulation leads to higher QTP levels in hippocampus.

Acknowledgments: CNPq/Brazil and CAPES/Brazil.

ARTHEMETER AND DOCOSAHEXAENOIC ACID CO-ENCAPSULATION IN NANOCARRIERS: DEVELOPMENT AND CHARACTERIZATION

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Introduction: Arthemeter (ART) showed anticancer activity in vitro and in vivo. The low water solubility, poor bioavailability, and a short half-life in vivo are the pharmacological shortcomings of ART. Literature shows that docosahexaenoic acid (DHA) may reduce the cancer cell growth. One strategy to overcome these challenges is the encapsulation of ART to improve the activity against cancer cells co-encapsulated with DHA. The aim of this study was the development and characterization of nanocapsule (NC-ART/DHA), nanoemulsion (NE-ART/DHA), nanostructured lipid carrier (NLC-ART/DHA) and self-nanoemulsifying drug delivery systems (SNEDD-ART/DHA) containing both molecules to carry out a comparative study of ART and DHA association with different carriers. Methods: NC-ART/DHA was prepared by nanoprecipitation method, NE-ART/DHA by spontaneous emulsification method and NLC-ART/DHA by hot homogenization method. The mean diameter, zeta potential and polydispersity index (Pdi) were determined by dynamic light scattering. Entrapment efficiency (EE) was determined by ultrafiltration/centrifugation technique. The nanoparticles were also evaluated for colloidal stability during 180 days storage. Results and discussion: All nanocarriers were monodispersed (Pdi the zeta potential for all formulations were negative. The particle size were in nanometric range (NC-ART/DHA=163±0.9; NE-ART/DHA=168±0.8; NLC-ART/DHA=196±1.5 and SNEDD-ART/DHA=145±0.8). The entrapment efficiency for ART in NC-ART/DHA, NE-ART/DHA and NLC-ART/DHA were 76%, 78% and 57%, respectively. Only the NLC-ART/DHA formulation wasn’t stable by 180 days. Conclusions: The results showed that the NC, NE and SNEDD are interesting systems to co-encapsulate lipophilic molecules, ART and DHA, with high encapsulation efficiency and colloidal stability on storage.

Financial support and acknowledgments: The authors thank CAPES, INCT-NANOFARMA (CAPES #2014/50928-2), FAPEMIG (APQ-02864-16), CNPq (310463/2015-7) and UFOP, Brazil, for financial support.
TISSUE DISTRIBUTION OF RESVERATROL IN WISTAR RATS

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Introduction: Resveratrol (RSV) is a polyphenolic antioxidant compound produced by a wide variety of plants including grapes, peanuts, blueberries and red wine being the most widespread and known source. Over the past decades, interest in studying RSV has grown due to its pharmacological effects related primarily to cardiovascular and neuroprotection. Therefore, this study aimed to study the tissue distribution of RSV after i.v. dosing in Wistar rats.

Methods: A dose of 10 mg.kg⁻¹ iv bolus of RSV was administered to Wistar rats, at 1h, 3h, 6h, 11h and 24h after administration the animals were euthanized (n = 3 / point) (CEUA/UFBA 043/16). Samples of the liver, lung, kidney, heart, stomach, spleen, adipose tissue and brain were removed, dried, weighed and frozen at -80 °C until processing. On the day of analysis, the tissue samples were allowed to thaw and homogenized with methanol for 5 min. The homogenates were then transferred to Eppendorf tubes and centrifuged at 3500 × g for 15 min at 4 °C. A volume of supernatant was analyzed by HPLC-UV using previously validated method.

Results and discussion: RSV showed high concentration values in the analyzed tissues, especially in the stomach, kidney, liver and adipose tissue. This molecule also shows high brain concentration in 3h after dosing.

Conclusions: RSV showed high tissue distribution and presented high brain levels, indicating that this molecule is able to cross the blood-brain barrier of Wistar rats a crucial capacity for its neuroprotective activity.

Financial Support: PROPCI-UFBA and MCTI

PRECLINICAL PHARMACOKINETICS OF RESVERATROL

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Introduction: Resveratrol (RSV) is synthesized by several plants under adverse factors. This polyphenol has attracted the attention of Pharmaceutical Sciences due to its various pharmacological effects. In this work we aimed to quantify RSV in plasma of Wistar rats after intravenous and oral administration in order to obtain its PK parameters.

Methods: After the administration of RSV at doses of 5mg/kg via i.v. bolus and 50 mg/kg orally to animals (n = 6/group), plasma collection was performed at intervals up to 24 hours (CEUA/UFBA 043/16). The collected plasma was analyzed by HPLC/UV using a validated method. From this analysis, plasma concentration values were obtained enabling the construction of concentration vs. time profiles and the calculation of the non-compartmental PK parameters.

Results and discussion: The values of ke were 0.09 ± 0.04 h⁻¹ and 0.12 ± 0.07 h⁻¹, t½ were 9.5 ± 3.7 h and 7.9 ± 4.2 h, Vd were 5.8 ± 4.7 L/kg and 13.3 ± 3.3 L/kg, CL were 0.39 ± 0.26 L/h/kg and 1.76 ± 0.49 L/h/kg, AUC0-∞ were 6076 ± 2959 and 6519 ± 1592 µg.h/mL, MRT values were 8.7 ± 3.4 h and 7.7 ± 1.7 h after iv and oral dosing, respectively. The calculated bioavailability was 6%. Conclusions: The RSV non-compartmental PK analysis showed that this molecule has good distribution resulting in higher half-life values than those of the literature. The evaluation of PK profiles indicate that this drug could perform a two compartment model in both administrations.

Financial support: PROPCI-UFBA and MCTI
EVALUATION OF THE ANTI-INFLAMMATORY AND TOXICOLOGICAL ACTIVITY OF AN N-ACYLHYDRAZONE DERIVATIVE

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N-acylhydrazonic derivatives are promising carbonic structures that contain important pharmacophore groups, which makes them strong drug candidates with anti-inflammatory activity. This study aimed to evaluate the anti-inflammatory and toxicological potential of the N-acylhydrazonic compound: 2-cyano-N’-[4-(methylsulfonyl) benzylidene] acetohydrazide. For the pharmacological tests, Swiss adult mice of both sexes were used. The models employed to evaluate the activity were peritonitis, foot edema and pocket of subcutaneous air, and the evaluation of the safety of use was verified by the test of acute toxicity of single dose. The results were expressed using the analysis of variance, followed by the Dunnet or Tukey test (Software GraphPad Prisma). The project was approved by the Animal Ethics Committee, number: 5905022016. In the carrageenan-induced peritonitis model, the compound JR04 showed an inhibition of leukocyte migration in 48.3 and 54.1%, at doses of 10 and 20 mg.kg⁻¹, respectively. As there was no significant difference between the two doses, the dose of 10 mg.kg⁻¹ was chosen for the other experiments. In the paw edema model, inhibition of edema was 76, 95 and 96% in the second, third and fourth hour, respectively. In the pockets of subcutaneous air, JR04 inhibited cell migration by 55%. In the evaluation of the acute toxicity of compound JR04 (100 mg.kg⁻¹) did not produce physiological or behavioral alteration, indicating low toxicity. The results obtained show the therapeutic potential of JR04 as anti-inflammatory, however, it is necessary to continue these studies to elucidate the possible mechanisms involved in the pharmacological response.

Support: CNPq and UEPB.

POTENTIALITIES AND LIMITATIONS OF THE DIET-INDUCED OBESE RAT MODEL IN TRANSLATING THE PROPHYLACTIC EFFECT OF CEFAZOLIN

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Introduction: Cefazolin (CFZ) is the antimicrobial prophylactic agent of choice for reducing the risk of surgical site infections (SSI) in obese patients undergoing bariatric surgery. The aim of this work is to evaluate the validity of using CFZ pharmacokinetic data from diet-induced obese rats to predict drug’s prophylactic outcomes in obese patients. Materials and methods: Obesity was induced in Wistar rats by hypercaloric diet (CEUA/UFRGS # 25463). CFZ total plasma and the free interstitial subcutaneous concentrations by microdialysis were determined following 30 or 45 mg/kg i.v. bolus doses. Datasets were used to develop CFZ popPK model for rats. The model was applied to predict human’s clinical outcomes as probability of target attainment (PTA) using Monte Carlo simulation. Different strategies were tested for the translation of outcomes. Results and discussion: The main limitations for translation were the differences in CFZ elimination, tissue penetration and free fraction at the site of action between obese rats and humans. A two compartments popPK model with saturable elimination pathway and saturable plasma and tissue CFZ binding to protein was developed to describe rat’s data. The translation strategy using popPK model with rat’s allometric scaled clearance and volume of distribution together with human’s protein binding constants was successful to obtained PTA outcomes similar to those previously published for humans (equivalence between 96.7 and 121.7%). Conclusions: A strategy was devised that allowed the translation of CFZ prophylactic outcomes in humans from rat’s data, helping the definition of best prophylactic dose for obese patients.

Acknowledgements: Financial support from PPSUS/FAPERGS 2013 (#1298-255/13-8).
**HISTORICAL ASPECTS OF PHARMACOLOGY ACCORDING TO A BIBLIOGRAPHIC REFERENCE OF EARLY-20TH CENTURY**

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**Introduction:** The development of pharmacology as a research area date back to the 18th century, compelled by advances in modern science. In late 19th century, it was consolidated as science and discipline, and progressively became mandatory for health care professionals. Motivated by the progress of pharmacology in the last century, we analyzed a 20th century pharmacology textbook regarding to toxic and/or illicit compounds used in therapy. **Methods:** We perlustrated 'Curso de Pharmacologia' (2nd edition, 1925/26), written by Professor Jovelino Mineiro. It is a compendium of pharmacology lessons from that time – preparation, purification, and potential falsifications of commonly used medicines then, such as mineral compounds, salts and organic acids, alkaloids and glycosides – taught by him at Ouro Preto School of Pharmacy. Our analysis focused on poisonous and/or illicit alkaloid compounds employed in therapy. **Results and discussion:** Nature’s resources – mainly from plants – were the sole medicine available to man until mid-19th century. Jovelino was confronted with a large number of natural drugs, but very few were safe based on modern point of view. Numerous strychnine, arsenic, heroin, morphine, and cocaine compounds were described as potent anesthetics, and fortifying tonics – considered for adult and pediatric use. Toxic effects were gradually described as of the second half of the 20th century. **Conclusions:** Alkaloid compounds were mostly used in early-20th century based on their known therapeutic properties. However, the toxic effects of these substances were not appraised, demonstrating that drug safety was not a priority until mid-20th century.

**Financial support:** FAPEMIG, UFOP, and CAPES.

**HYDROQUINONE IS A POTENTIAL COMPONENT OF CIGARETTE SMOKE WHICH WORSEN RHEUMATOID ARTHRITIS IN RATS**

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**Introduction:** Collagen-induced arthritis (CIA) is accepted as an animal model for mimicking rheumatoid arthritis (RA), a chronic autoimmune disease. Studies indicate an association of smoking with arthritis outcome. Hydroquinone (HQ) is a phenolic compound, found in high concentrations in cigarette and is a benzene metabolite. Herein, we investigated the role of HQ exposure on CIA and the involved mechanisms. **Methods:** Animals were immunized at the tail with bovine type II collagen emulsified with complete Freund’s adjuvant. A booster was administered 7 days later. Rats were exposed to saline, vehicle (saline-ethanol 20:1) or HQ 25ppm, 1 hour/day, using a nebulization chamber, according to: A – during 35 days (days 1 to 35); B – during the sensitization phase (days 1 to 14); C – after CIA development (days 29 to 35). On day 35, animals were euthanized and submitted to clinical evaluation, histological analysis of the synovia and quantification of cytokines. Data were obtained in 4 animals per group (CEUA/USP 435). **Results/Discussion:** HQ exposure elevated clinical parameters of CIA; augmented levels of IL-6 and IL-1β in fluids; increased inflammation in the synovia, characterized by pannus formation and collagen deposition, increased neutrophil influx and enhanced AhR expression and IL-17 levels. Additionally, HQ in vitro treatment augmented AhR expression and IL-17 production by splenocytes and neutrophils and administration of an AhR antagonist blocked these effects. **Conclusion:** we show that HQ, as an important component of cigarette smoke, aggravates CIA in rats and the activation of AhR/IL-17 pathway is a possible mechanism involved in the RA pathogenesis. **Financial support:** CNPQ; FAPESP (2014/07328-4).
MODULATION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR $\gamma$ BY ANNEXIN A1 IN A MICROGLIAL CELL LINE

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Introduction: Peroxisome proliferator-activated receptor $\gamma$ (PPAR$\gamma$) is a nuclear protein expressed in immune cells, including those in the central nervous system (CNS). Annexin A1 (ANXA1) is an anti-inflammatory protein involved with glucocorticoid-mediated effects, also expressed in immune cells of the CNS. Both PPAR$\gamma$ and ANXA1 display anti-inflammatory actions and might contribute to alleviation of inflammation in the CNS, but the underlying mechanisms and interactions with other anti-inflammatory factors that lead to such actions are not fully understood.

Methodology: BV2 cells (murine microglia), unadulterated or transfected with plasmids aimed to down-regulate ANXA1 expression, were treated with exogenous ANXA1. Protein and gene expression of PPAR$\gamma$ were assessed. Expression and phosphorylation of STAT6, a transcription factor, were also investigated. In order to assess the effects of the ANXA1-PPAR$\gamma$ interaction, BV2 cells treated with either ANXA1, GW9962 (PPAR$\gamma$ antagonist) or both were co-cultured with apoptotic PC12 cells (murine neuron-like cell line); phagocytosis and expression of CD-36, a surface protein involved with phagocytosis and directly modulated by PPAR$\gamma$, were then assessed.

Results and discussion: Data obtained demonstrated that ANXA1 increases expression of PPAR$\gamma$ in BV2 cells, while its lack decreases such expression; lack of ANXA1 also decreases STAT6 expression and phosphorylation. Even though treatment with ANXA1 did not modulate CD36 expression, it increased phagocytosis of apoptotic cells, and such effect was abolished by blockade of PPAR$\gamma$.

Conclusions: Our data show that ANXA1 modulates PPAR$\gamma$ expression in BV2 cells, and it also suggests such interaction might play a role on control of phagocytosis.

METHYL CHAVICOL INHIBITS SKIN INFLAMMATION INDUCED BY IRRITANTS

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Introduction: Methyl chavicol (MC) is a phenylpropanoid found in essential oils and has been known for its antimicrobial, anti-inflammatory and local anesthetic properties. In this study, the topical anti-inflammatory activity of MC was evaluated using in vivo and in vitro assays.

Methods: Topical anti-inflammatory activity was evaluated by Croton oil-, phenol-, histamine- and capsaicin-induced ear edema in mice after treatment with 0.1, 0.5 and 1.0 mg/ear (n = 6). Histopathological analysis and myeloperoxidase (MPO), N-acetyl-β-D-glucosaminidase (NAG), nitric oxide and cytokines assays were performed. The procedures were approved by the Institutional Ethics Committee (protocol number 038/2015).

Results and discussion: MC decreased the ear edema thickness induced by Croton oil after 6 (58.02 to 67.75%) and 24 h (68.65 to 81.95%) of treatment ($p < 0.001$). In 24 h, the ear edema weight (56.16 to 70.55%) was also reduced. MC inhibited the ear edema thickness (65.71 to 67.96%) and weight (21.96 to 23.45%) induced by phenol ($p < 0.001$). After histamine-induced ear edema, MC reduced the thickness (12.60 to 72.65%), while the weight was inhibited from 23.09 to 86.08% ($p < 0.001$). In capsaicin test, the ear edema thickness (57.07 to 68.43%) and weight (65.50 to 68.16%) were reduced by MC ($p < 0.001$). Histopathological analysis revealed that MC reduced the inflammatory parameters, as well as decreased MPO, NAG, NO, TNF-α and IL-6 levels.

Conclusions: The results suggest that MC is effective against cutaneous damage, which can justify its therapeutic use for the treatment of skin disorders.

Financial support and acknowledgements: CAPES, FAPEMIG, CNPq and UFJF.
ANTIDIABETIC ACTIVITY OF BUTANOL FRACTION OF CALYCES FROM Physalis peruviana IN STREPTOZOTOCIN-INDUCED DIABETIC MICE

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Introduction: Physalis peruviana fruits and leaves has been used for traditional medicine in diabetes treatment for its hyperglycemic and antioxidant properties attributed to the content of phenolic compounds. The aim of this work was to evaluate the effect of the butanol fraction of calyces of P. peruviana on the blood glucose levels (BGL), lipid profile and oxidative stress markers.

Methods: Diabetes was induced in Swiss ICR mice by streptozotocin (150mg/kg). Diabetic mice (BGL > 200 mg/dL) were grouped into three treatments and administrated p.o. for 14 days. Group I: (distilled water), Group II: Glibenclamide (200mg/kg) and Group III: Butanol fraction of P. peruviana calyces (50mg/kg). Blood glucose levels and serum lipid profile were measured by 14 days. At the end of the experiment, animals were euthanized and malonyl dialdehyde, reduced glutathione, catalase and superoxide dismutase were measured in different organs.

Results: Significantly decrease of serum lipid profile and BGL were observed in the group treated with the butanol fraction (p < 0.05).

Conclusions: The butanol fraction from calyces of P. peruviana improved oxidative stress status and decreased levels of BGL and serum lipid profile in streptozotocin-induced diabetes mice. These results suggest the butanol fraction from calyces of P. peruviana as a promising alternative in the treatment of diabetes. All the experimental procedures were approved by Ethic Committee of the Universidad Nacional of Colombia, Sciences Faculty (14/2017).

Acknowledgements: DIB UNAL and Colciencias for financing the project “Preclinical evaluation of a microencapsulated extract from Physalis peruviana calyces with potential use in the treatment of diabetes mellitus” 677-2014 contract.

ARE CIPROFLOXACIN FREE BRONCHIAL CONCENTRATIONS INFLUENCED BY PULMONARY INFECTION STAGES?

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Introduction: We previously observed a reduction on ciprofloxacin (CIP) free pulmonary concentrations comparing healthy to acute and chronically biofilm-forming Pseudomonas aeruginosa infected rats. In this study, we evaluate CIP free bronchial concentrations in different stages of biofilm-forming P. aeruginosa lung infection.

Methods: Approved by UFRGS’ CEUA (#31651). Acute (2 days, 10⁸ UFC/mL of P. aeruginosa PA14) and chronic (14 days, 10⁹ UFC/mL of P. aeruginosa ATCC 27853 embedded in alginate beads) pneumonia were developed in male Wistar rats through intratracheal administration; healthy and blank beads control groups were used (n = 5-8/group). For bronchial microdialysis calibrated custom-made probes (CMA 20, 2 mm) were introduced into anesthetized rat bronchi and equilibrated for 1 h (Ringer solution, 1.5 µL/min) before CIP administration (20 mg/kg, i.v. bolus). Microdialysate (every 30 min) and plasma samples, collected up to 12 h post-dose, were analyzed by a validated HPLC/fluorescence method. Non-compartmental analysis was performed using Phoenix® v. 6.4 and statistics using Graphpad®.

Results: Bronchial exposition to CIP was similar in all groups (AUChealthy = 7.29 ± 2.44 µg·h/mL; AUCblank bead = 8.62 ± 5.07 µg·h/mL; AUCacute = 5.59 ± 3.26 µg·h/mL; AUCchronic = 5.44 ± 2.16 µg·h/mL) (p > 0.05). In healthy and acutely infected groups bronchial exposition equivalent to 46% of pulmonary free levels was observed. This ratio was increased to 65% in chronically infected groups. Conclusions: Although free CIP pulmonary concentrations decrease with infection advance, free bronchial concentrations are not affected by the disease, showing a relative increase in chronic stage when compared to pulmonary free levels.

Financial support: CNPq/Brazil, CAPES/Brazil.
QUANTIFICATION OF TRACE METALS IN BEERS

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Introduction: Beers may have in their compositions substances considered as non-beneficial to human health, such as toxic metals in trace levels, either from the raw materials or from the packings. Although the content of trace metals can be low for a single dose, the continued exposure of toxic elements increases the risks of potential bio-magnification effect on body tissues.

Methods: The following potential toxic elements were quantified in 10 beers by inductively coupled plasma mass spectrometry (ICP-MS): aluminum (Al), beryllium (Be), titanium (Ti), nickel (Ni), arsenic (As), antimony (Sb), tellurium (Te), barium (Ba), tungsten (W), thallium (Tl), silver (Ag), cadmium (Cd), tin (Sn), lead (Pb), bismuth (Bi), uranium (U) and mercury (Hg).

Results and discussion: Seven samples showed values above the acceptance concentrations/day by World Health Organization (WHO) and other governmental agencies as FDA and ANVISA. Sample II mercury concentration = 0.006 mg/L (limit 0,005 mg/L). Sample VII silver concentration = 0.110 mg/L (limit 0.08 mg/L). Sample IV thallium concentration = 0.00018 mg/L (limit 0.00010 mg/L). For titanium (limit 0.015 mg/L), the sample concentrations were IV = 0.066 mg/L; V = 0.052 mg/L; VI = 0.095 mg/L; VII =0.051 mg/L; VIII = 0.045 mg/L; and IX = 0.053 mg/L. The values found for the other elements tested were within the limits of acceptance.

Conclusion: 70% of the beers analyzed presented high concentration levels of at least one toxic element. Intake of these elements above the acceptance concentrations can pose a threat when consumed chronically.

INHIBITORY EFFECT OF SYNTHETIC AMINO ACID DERIVATIVES ON THE PANCREATIC LIPASE

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Introduction: Pancreatic lipase is an enzyme that hydrolyses ester linkages of triglycerides with release of fatty acids to be absorbed. The use of synthetic and natural drugs that inhibit this enzyme, such as orlistat, has been clinically useful for the treatment of obesity. The present work aimed to evaluate the inhibitory effect of synthetic amino acid derivatives (PPC82, PPC80 and PPC89) on the pancreatic lipase activity.

Methods: Lipase inhibition assays were performed by photometric method using a microplate reader. Orlistat (1 mg/mL), PPC82 (1 mg/mL), PPC80 (10 mg/mL) and PPC89 (10 mg/mL) were evaluated. The reaction was performed with suine pancreatic lipase (100 μL), synthetic derivatives or orlistat (50 μL) and p-nitrophenolpalmitate (substrate, 50 μL). The mixture was incubated in a 37°C water bath at the times of 10, 20, 30, and 40 minutes. The absorbance of the reaction product (p-nitrophenol, yellow coloration) was determined at 405 nm.

Results and discussion: Orlistat (1 mg/ml), positive control, produced 70.18% inhibition of pancreatic lipase activity, while PPC80 (10 mg/mL) and PPC89 (10 mg/mL) inhibited 54.39% and 84.21% of the enzymatic activity, respectively (p < 0.001). In this assay, PPC89 (10 mg/mL) was not active on the enzyme which may be due to the presence of 8 carbons in the aliphatic chain.

Conclusions: The results suggest that PPC82 and PPC80 are capable of inhibiting pancreatic lipase activity and may be novel therapeutic compounds for the treatment of obesity and metabolic disorders.

Financial support and acknowledgements: CAPES, FAPEMIG, CNPq and UFJF.
ABCG2/BCRP c.421C>A POLYMORPHISM ALTERS NIFEDIPINE TRANSPORT TO BREAST MILK IN CHRONIC HYPERTENSIVE BREASTFEEDING WOMEN

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Introduction: The breast cancer resistance protein (BCRP) human transporter, encoded by the ABCG2 gene, is highly expressed on the human lactating breast. Nifedipine, a known substrate of BCRP, is used for the treatment of hypertension in pregnancy and during breastfeeding. BCRP plays an important role in secreting drugs and xenobiotics into milk. The single nucleotide polymorphism (SNP) c.421C>A is associated with lower expression of BCRP in the placenta. The aim of the present study was to evaluate the effect of ABCG2 c.421C>A on nifedipine breast milk/plasma concentration ratio in hypertensive breastfeeding women (HBW).

Methods: The study protocol was approved by the hospital ethical committee (CAAE 50836415.6.3001.5440, n° 1.332.596). Nineteen HBW treated with 20 mg slow-release nifedipine every 12 hours were investigated. Blood and breast milk samples were collected simultaneously 15-30 days after delivery and at least 15 days after drug treatment, in order to reach drug steady state. All patients were genotyped for ABCG2 c.421C>A using RT-PCR. Nifedipine concentration was determined in plasma and breast milk by high-performance liquid chromatography using UV detection.

Results and discussion: Patients genotyped as 421CC showed nifedipine plasma concentrations ranging from 8.32 to 178.1 ng/mL (median: 44.3 ng/mL), whereas milk concentration ranged from 4.8 to 58.5 ng/mL (median: 10.5 ng/mL). Lack of correlation was observed between nifedipine plasma and breast milk concentrations (Spearman r=0,12; p=0,62). Nifedipine breast milk/plasma concentration ratio was significantly lower in 421CC (n=13, median: 0.73) when compared to 421CA (n=6; median: 1,20; p = 0.01). The comprehension of the variability in the transport of nifedipine to breast milk in HBW will contribute to the evaluation of drug exposure in neonates and infants to nifedipine and other ABCG2 substrates. Conclusion: ABCG2/BCRP c.421C>A polymorphism is associated with a higher transfer of nifedipine to breast milk.

Financial support: CAPES; Pró-Reitoria de Pesquisa da UNESP (Edital 009/2016)

MACROPHAGES BEHAVIOR IS INFLUENCED BY HIGH GLUCOSE UNDER LPS STIMULUS

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Introduction: Hyperglycemia is one of the main sources of complications in diabetic subjects contributing to a high susceptibility to infections. A hyperglycemic environment may affect macrophages responses upon stimulation. Herein we hypothesized that hyperglycemia could change the way macrophages respond to lipopolysaccharide (LPS) stimulus. Methods: Bone marrow-derived macrophages (BMDM) from non-diabetic (saline) and diabetic (aloxan 60 mg/kg, i.v) male C57BL/6 mice (CEUA/FCF/USP-488). BMDM were exposed to a normal glucose (5,5 mM) (NG) and high glucose (25 and 40 mM) (HG) media and stimulated with LPS (100 ng/mL). It was measured TLR4 expression, phagocytosis, intracellular protein of LPS pathway, H_2O_2 and NO release.

Results and discussion: BMDM from diabetic mice expressed less TLR4 under LPS stimulus with higher phosphorylation at phospho-PI3K p85 and released less NO and H_2O_2 with and without LPS. When diabetic BMM were cultured in HG, they phosphorylated less in PKC-δ and in p46 SAPK/JNK, but when stimulated by LPS, they phosphorylated more in p46 SAPK/JNK. Conclusions: High glucose (hyperglycaemic environment) seems to modify macrophages behaviour, affecting in different aspects diabetic and normal BMDM under the same LPS stimulus. Financial support: FAPESP (2017/11540-7), CAPES and CNPq (301617/2016-3).
PHARMACOKINETIC PROFILE OF INDINAVIR IN RATS

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Introduction: Indinavir is an antiretroviral drug used in adult patients which requires further research for derivation of pediatric forms. The present work aims to evaluate the potential of nanotechnology application in the improvement of pharmacokinetic and organoleptic characteristics of Indinavir. Method: The plasma pharmacokinetics of Indinavir was evaluated in Wistar rats (n = 5) weighing 250-350g after administration of an intravenous dose of 15 mg/kg which will be applied in the future studies to determine the bioavailability of ID in oral solution and in nanocapsules’s suspension. Firstly a HPLC-UV methodology was validated to determine the plasma concentrations. After the administration, plasma samples were harvested from the lateral tail vein at 0.08, 0.16, 0.0.75, 2, 6, 12, 18 h after dosing. Data analysis was performed by non-compartmental and compartmental analysis using Phoenix®. Results and discussion: The model which best describes the pharmacokinetics of indinavir in rodents was the two-compartmental model, showing a good agreement between the parameters AUC0-0.08, Vdss, half-life and CL defined to both approaches. The values of theses parameters were: 130.17 ± 22.51 and 98.71 ± 20.70 ug.h/mL, 2675.51 ± 1725.28 and 1137.01 ± 647.09 mL/kg, 13.15 ± 5.70 and 8.40 ± 6.23, 174.67 ± 39.56 and 156.53 ± 27.20 mL/h/kg, respectively. Conclusion: Indinavir showed high variability on its pharmacokinetic parameters in rodents like other antiretroviral drugs. These results will be useful to further investigations about the pharmacokinetics of indinavir in rodents in the next steps of this work allowing the determination of drug’s bioavailability in new formulations.

Financial support: CNpq, Capes.

Ethical approval: Ethics Committee in the use of animals - UFRGS # 20353.

References:

INSULIN SELECTIVELY AFFECTS LPS-INDUCED CYTOKINE SECRETION BY MACROPHAGES FROM TYPE 1 DIABETIC MICE

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Introduction: Low levels of insulin or high levels of glucose are commons effects on diabetes and it can cause a dysregulation in Toll-like receptor (TLR4) signal transduction in macrophages generating an impaired response to microorganisms. Methods: Bone marrow-derived macrophages from male non-diabetic (BMDM) and diabetic C57BL/6 mice (BMDM-D) (alloxan 60 mg/kg, i.v., CEUA/FCF/USP - 467) were stimulated or not by lipopolysaccharide (LPS - 0.1 ug/mL and 1 ug/mL) and treated or not by insulin (1 mU/mL). BMDM was stimulated by LPS (0.1 ug/mL) and simultaneously treated with insulin. Results and discussion: With no stimuli, BMDM-D expressed more levels of PI3Kalpha and p-Akt (Ser-473 and Thr-308), p-ERK 1/2 MAPK and FAPES (2017/11540-7), CAPES and CNPq (301617/2016-3).

Conclusion: Compared to BMDM, BMDM-D presented an impaired response to LPS in the first and second stimuli, and insulin increased LPS-induced cytokine secretion via PI3K and ERK1/2.

Financial support: FAPESP (2017/11540-7), CAPES and CNPq (301617/2016-3).
PHARMACOGENETICS-BASED POPULATION PHARMACOKINETIC ANALYSIS OF GABAPENTIN IN PATIENTS WITH CHRONIC PAIN: EFFECT OF OCT2 AND OCTN1 GENE POLYMORPHISMS

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Introduction: Gabapentin (GAB), used to treat chronic pain, presents nonlinear kinetics and is eliminated unchanged in urine. The organic cation transporters OCT2 and OCTN1 have been shown to play a role at GAB renal excretion. This prospective clinical study aimed to evaluate OCT2 and OCTN1 genetic polymorphisms effect on GAB pharmacokinetics. Methods: Data were collected from fifty-three patients with chronic pain receiving multiple doses of GAB for at least 7 days (ClinicalTrials.gov Identifier: NCT02977208). Patients were genotyped for SLC22A2 c.808G>T (rs316019) and SLC22A4 c.1507C>T (rs1050152) polymorphisms. Population pharmacokinetic analysis was performed using non-linear mixed effect modelling to investigate the influence of genetic polymorphisms on between-subject variability of kinetic disposition of GAB. Results and discussion: The genotypes of both polymorphisms were at Hardy-Weinberg equilibrium. The minor allele frequencies of SLC22A2 c.808G>T and SLC22A4 c.1507C>T were 6% and 33%, respectively. A one-compartment model with first-order absorption and linear elimination best described the data. The population parameters estimated with the final model were: first-order absorption constant (ka)= 0.44 h⁻¹; volume of distribution (Vd/F)= 86 L and clearance (Cl/F)= 17.3x(estimated glomerular filtration ratio/mean)⁻¹. Only eGFR affected the clearance and contributed to explain interindividual variability. Gene polymorphisms of OCT2 and OCTN1 did not had a significant influence on GAB distribution or elimination. Conclusion: Gabapentin clinical pharmacokinetics is strongly influenced by renal function and not by the pharmacogenetics of OCT2 and OCTN1.

Ethical approval: Faculdade de Ciências Farmacêuticas da UNESP (CAAE: 53902516.4.0000.5426) and Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto (CAAE: 53902516.4.3001.5440).

Financial support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Programa de Apoio ao Desenvolvimento Científico (PADC – FCF, UNESP) and Pró-Reitoria de Pós-Graduação da UNESP (PROPG).

FOOD IMPACT ON TENOFOVIR DISOPROXIL FUMARATE PHARMACOKINETICS

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Introduction: Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse-transcriptase inhibitor used in combination with other antiretroviral agents for the treatment of HIV infection. For TDF, the effect of food was explored in HIV-infected patients and in healthy volunteers. While information regarding food intake and TDF pharmacokinetics exists, it is lacking for the Brazilian population, characterized by extensive miscegenation. So, the primary objective of this study was to evaluate the pharmacokinetics of TDF under fasted and fed conditions in Brazilian volunteers. Methods: This was a single-center, open-label pharmacokinetic study of TDF in fasted and fed state; 72 healthy Brazilian volunteers were included, 36 in each group. TDF was administered in a single dose (300mg) and plasma collected up to 71 hours later. This study was approved by the Ethics Committee of the Health Sciences Center/UFPE (CAAE 0276.0.172.000-10 and 0109.0.172.000-10). ANOVA were conducted to verify differences between groups. Results and discussion: Mean[SD] pharmacokinetic parameters for participants in the fasted and fed groups were as follows: Cmax 300.55[115.68] and 309.02[95.52] µg.mL⁻¹, AUC∞0.2124.92[705.82] and 3020.23[679.03] µg.h.mL⁻¹, AUC0-∞ 2361.04[765.67] and 3298.69[699.44] µg.h.mL⁻¹, Tmax 0.86[0.58] and 2.19[1.08] h and t1/2 16.88[5.44] and 19.67[6.23] h, respectively. The AUClast, AUC0-∞, Tmax, and t1/2 values of TDF showed statistically significant increases when administered in a fed state; however, there was no change in the Cmax value, as described in literature. Conclusions: Food intake showed increased bioavailability of TDF, which may increase the treatment toxicity since there is no restriction about food impact in TDF practiced posology.

Acknowledgements: We thank Farmácia Escola Carlos Drummond de Andrade and Núcleo de Desenvolvimento Farmacêutico e Cosmético/CCS/UFPE.
INFLUENCE OF EPILEPSY IN EXPRESSION OF TRANSPORTERS

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Introduction: Epilepsy is a worldwide spread pathology prevalent in developing countries; about fifty million people in the world are affected by this pathology. The disease is characterized by recurrent seizures, which are brief episodes of involuntary movements of the body, occurring due to excessive electrical discharges that affect the brain cells. Patients who have epilepsy, in some cases don’t respond successfully to the treatment. Some carriers, such as the P-glycoprotein (Pg-P), present in the blood brain barrier may be involved in resistance mechanisms to antiepileptic drugs, which are substrates of Pg-P. Therefore, the evaluation of Pg-P expression and activity may help to understand epilepsy’s pathological mechanisms.

Methods: The evaluation was performed comparing healthy animals and others presenting genetic background susceptible to the development of epilepsy, wistar audiogenic rats (WAR) wich received fexofenadine (dose of 10mg/kg, oral gavage), a Pg-P substrate, collecting blood, from 0 until 12 hours after administration (Protocol Ethics Committee nº 658/2015 CEUA-UNIFAL/MG).

Results and discussions: The pharmacokinetic analysis results, showed an increase in fexofenadine bioavailability (AUC) and half-life due to a clearance reduction in WAR-resistant to seizures (p < 0.05).

Conclusions: This change in Pg-P expression may be responsible for pharmacokinetic alterations on the WAR resistant group, as soon as the drug distribution into the CNS was reduced, and this finding may be one of the causes for the pharmacological treatment failure observed in the patients.

CHRONIC TREATMENT WITH CINNAMALDEHYDE PREVENTS SPONTANEOUS ATHEROSCLEROTIC PLAQUE DEVELOPMENT IN OVARIECTOMIZED LDLR-/- FEMALE MICE

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Introduction: Cardiovascular diseases, which occur subsequent to atherosclerosis, are the main cause of death worldwide. Endogenous estrogen protects against these diseases. However, postmenopausal women lose this protection. Cinnamaldehyde, the main bioactive compound found in Asiatic cinnamon bark oil, has shown beneficial effects against cardiovascular diseases. The present study investigated the effects of cinnamaldehyde on atherosclerotic lesion development, lipid profiles and oxidative stress markers in ovariecomized LDLr-/- female mice, with access to water and standard feed ad libitum, without the use of an atherogenic diet.

Methods: Female mice were treated with cinnamaldehyde (20 mg/kg body weight/day) for eight weeks. Lipid deposition in the aortas was determined by the en face method and oil red staining. Lipid profiles and oxidized LDL levels were analyzed in the blood samples, and oxidative stress markers were analyzed in the hepatic tissue samples.

Results and discussion: The data showed that ovariecomy induced lipid deposition in the aortas of female mice and treatment with cinnamaldehyde prevented the development of atherosclerotic lesions, regardless of changes in plasma cholesterol levels. Cinnamaldehyde reduced triglyceride levels and protein oxidation (AOPP) in both non-ovariectomized and ovariecomized animals. In addition, it reduced lipid peroxidation (TBARS) levels in the ovariecomized group. Cinnamaldehyde treatment also improved the activity of antioxidant enzymes (SOD and CAT) and reduced the levels of oxidized LDL.

Conclusions: Chronic cinnamaldehyde administration prevented atherosclerotic lesion development in the aortas of ovariecomized LDLr-/- mice, independent of plasma cholesterol levels, and this effect may be justified, at least in part, by its antioxidant activity.

Ethical aspects: Experimentation guidelines from the National Council for the Control of Animal Experimentation (CONCEA) and approved by the Ethics, Bioethics and Animal Welfare Committee of Vila Velha University (CEUA-UVV, 397/2016).

Acknowledgments: This research was supported by the Foundation for the Support of Research and Innovation of the Espírito Santo State (FAPES) and the Coordination for the Enhancement of Higher Education Personnel (CAPES).
OXANDROLONE INDUCES CARDIAC REMODELING WITHOUT CHANGE OF AUTONOMIC TONUS

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Introduction: Oxandrolone (OXA) is an anabolic androgenic steroid used in clinical practice for treatment of growth disorders in boys and girls during childhood. Thus, the aim of the present study was to evaluate the effects of oxandrolone treatment, on cardiovascular system of young male rats, using therapeutic doses. Methods: Male rats ageing 30 days were treated with OXA (0.25mg/kg/4weeks) or vehicle (carboxymethylcellulose; CON) by gavage. After 4 weeks of treatment, the autonomic tonus was evaluated by tachycardia or bradycardia responses that were elicited after atropine and atenolol administration (2 and 4mg/kg, respectively). Histological analyses of left ventricle (LV) of the animals were performed using H&E and Picrosirius-red stained. The study was approved by ethics committee (CEUA-UFES #10/2016). Results: OXA treatment had no effect on the MAP (CON=107.7±12.7; OXA=104.4±15.9mmHg) and basal HR (CON=362±26; OXA=349±20bpm), also OXA did not influence sympathetic (CON=143±20; OXA=121±35bpm) or parasympathetic (CON=-41.43±26.05; OXA=-64.57±46.56bpm) cardiac autonomic control. Histological analyses demonstrated that there was myocyte hypertrophy (CON=23.70±2.00; OXA=19.03±1.49 myocyte nuclei/field; \textit{pp Conclusions}: Treatment with OXA did not promote change on physiological control of cardiac reflex, however, it can produce a microscopic hypertrophy associated with cardiac remodeling, that indicates that even on therapeutic doses microscopic changes can be promoted, that after chronic use can contributes to deleterious effects on cardiovascular system by that drug.

EVALUATION OF THE MUTAGENIC AND ANTIMUTAGENIC EFFECT OF HYDROXYCUMARINS IN PERIODIC BLOOD OF SWISS MICE

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Introduction: Coumarins are molecules derived from phenolic compounds that present versatile pharmacological activities. Despite the diverse biological activities and widespread use, research on their genotoxicity or protective effects are contradictory. Thus, the objective of this study was to evaluate the mutagenic and antimutagenic activities of 3-hydroxycoumarin, 4-hydroxycoumarin, 6-hydroxycoumarin and 7-hydroxycoumarin compounds. Methods: The Micronucleus Test was carried out for mutagenicity, antimutagenicity and Nuclear Division Index (IDN). Swiss mice were treated orally with three different doses (50, 100 and 200mg / kg). Cyclophosphamide was used as an inducer of chromosomal damage. After 24 hours, the presence of micronuclei in 2000 polychromatic erythrocytes per animal was analyzed. (Protocol 034/2016 approved by CEUA-UFSJ). Results and discussion: There was no increase in micronucleus induction between the groups treated with the different doses of hydroxycoumarins when compared to the negative control, indicating no mutagenic effect. Regarding the antimutagenic effects, all coumarins showed a protective effect against the genotoxic action of cyclophosphamide. In addition, analysis of the Nuclear Division Index showed no cytotoxicity since there was no significant reduction of polychromatic erythrocytes in relation to the total erythrocytes of the groups when compared to the negative control. These effects may be related to their ability to eliminate free radicals, due to their antioxidant activities, which demonstrates their importance as promising compounds for pharmacological use. Conclusion: Hydroxycoumarins are not mutagenic compounds and exert a protective effect against chromosomal damage induced by cyclophosphamide, under the conditions used in this study. Financial support: CAPES.
THE IMMUNOREGULATORY EFFECT OF LIPID-CORE NANOCAPSULES IN HUMAN LEUKOCYTES

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Introduction: Lipid-core nanocapsules (LNCs), vesicular structures containing an oil core surrounded by a polymeric wall, represent a promising tool for therapy application. However, the immunomodulatory potential of this nanocapsule is not completely explored. Recently, was shown that LNC-pretreated melanoma cells increased the anti-tumor neutrophils response in a co-culture model. Herein, we investigated the LNCs effects on cell viability, cytokines secretion and MAPK signaling in human peripheral blood mononuclear cells (PBMCs). Methods: PBMCs from healthy donors were isolated by density gradient centrifugation (CEP Approval n° 52267215.2.0000.0067). LNC uptake was performed using CytoViva® microscopy. Cell viability was assessed by Propidium Iodide/Annexin V incorporation. Immunoassay was used to measure cytokines release. Results and discussion: LNCs were internalized by PBMCs cultured for 2 and 24 h. At increasing concentrations up to 0.5 × 10¹² particles/mL, LNCs not altered the cell viability in 24 h of culture. At same conditions, the IL-8, TNF-α and IL-10 release was decreased, while IL-6 and IFN-γ release were not altered. LNC did not modify the monocytes or T cell surface markers. In PBMCs stimulated with lipopolysaccharide (LPS, 5 μg/mL) or Concanavalin A (Con A, 10 μg/mL) plus LNCs, TNF-α and IL-10 secretion was decreased. Furthermore, the cytokines release reduction induced by LNC at basal or stimulated condition was associated with the inhibition of ERK1/2 phosphorylation. Conclusions: In summary, LNCs show an immunoregulatory action, downregulating the release of cytokines. These findings are of particular value to defining the application of this nanocapsule to a specific biomedical purpose based on its interaction with immune cells and immunoregulation.

Financial support: FAPESP 2014/07328-4 and PNPD-CAPES Fellowship.

STANOZOLOL PROMOTES LIPID DEPOSITION AND INFLAMMATORY IMBALANCE ON LDL KNOCKOUT MICE

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Introduction: Stanozolol is an anabolic androgenic steroid used with aesthetic proposes. The aim was to evaluate the effect of stanozolol in a model of atherosclerosis and investigate the involvement of inflammation and oxidative stress on vascular lipid deposition. Methods: LDLr⁻/- mice were separated into two groups: C (n=8), received saline (vehicle for stanozolol); S (n=8), received stanozolol (20mg/kg/week, s.c.). All groups were fed a standard chow diet, and the treatments were performed for 8 weeks (CEUA-UVV:338/2014). At the end of the experiment, the levels of cholesterol, oxidized LDL (OxLDL) and cytokines were measured in plasma, lipid deposition in aorta was determined by en face analysis, TBARS and AOPP were determined in liver. Results: The S group demonstrated increases in vascular lipid deposition, triglycerides and non-HDL cholesterol levels. Stanozolol promoted an imbalance of cytokines, as demonstrated by an increase in the TNF-α/IL-10 ratio, which demonstrated a systemic inflammatory status. Furthermore, oxidative stress was observed in the S group, as indicated by an increase in the plasma OxLDL, as well as by lipid peroxidation and oxidation of proteins in the liver. Conclusion: Chronic treatment with stanozolol promoted lipid deposition in the LDLr⁻/- mice that could be attributed to a modification of the circulating cytokine status and systemic oxidative stress. The deleterious effects observed provide new data and suggest that the absence of function of the LDL receptor associated with the use of high doses of stanozolol could increase the risk for the development and progression of atherosclerosis independent of a western diet.
Bromopride (BRO) is a prokinetic and antiemetic drug used to treat digestive disorders, nausea, vomiting and gastroesophageal reflux disease, since early eighties. Although its prescription is common in Brazil, we have little studies about pharmacokinetic of BRO. The aim of this study was to investigate the population pharmacokinetic absorption profile of BRO. The data were collected from Bromopride’s bioequivalence studies presented to Brazilian Health Surveillance Agency. The data were modeled using MONOLIX 2018R1 software. Different structural models, like zero- and first-order (with and without a lag time), transit compartment, parallel first order, and mixed absorption, all of them with one-compartment disposition and linear elimination, were evaluated to find which one best describes the plasma concentration-time profile after oral administration of bromopride’s capsule. According to the goodness-of-fit (diagnostic plots, Bayesian information criteria and log-likelihood), the best model to describe the absorption process of BRO was zero order with lag time. Typical parameters estimates were duration of the zero-order absorption (Tk0) of 0.931 h with a lag time (Tlag) of 0.456 h, a volume of distribution (Vd) of 6.01 l/kg and a clearance (Cl) of 0.808 l/h/kg. Zero-order models are reasonable to describe absorption process of drugs whose input is influenced by solubility, like BRO. According to the literature the plasma protein binding rate of BRO was 40%, so this large Vd implied extensive binding of the drug in tissues. The renal clearance is similar to glomerular filtration rate and represent only 10% of the sistemic Cl. As far as we know this is the first time that the population pharmacokinetic absorption model was described for BRO.

Circadian rhythms play a critical role on the absorption, distribution, metabolism and excretion of many drugs in clinical practice. Benznidazole (BNZ), current specific chemotherapeutic drug for Chagas’s disease, is far from ideal due to multiple side effects and variable efficacy, especially in the chronic phase of disease. To date, limited data on the BNZ pharmacokinetics (PK) are available. The dog has been proposed as a good model in Chagas’s disease to translate the pathology aspects and efficacy of drugs in clinical trials. The objective of the present study was to evaluate the influence of dosing-time on the BNZ PK in dogs. Eight healthy undefined breed dogs (age = 12-24 months; mean weight = 22kg) received a multiple oral dose of 3.5 mg/kg/12h BNZ (LAFEPE, Brazil) on fed stomach (CEUA/UFOP:2016/37). Serial blood samples were collected at steady state (interval of 12hs) after administration either at 7:00 am or 7:00 pm. BNZ serum concentrations were measured using HPLC-DAD. The non-compartmental PK parameters were calculated using Phoenix WinNonlin version 7.0 software and compared using the Mann-Whitney test (p ≤ 0.05). After BNZ administration in different dosing-time, the PK parameters including, Kd, Cmax, Cmin, T1/2, AUC0-12h, Vd/F, CL/F, Kd, t1/2, fluctuation index and accumulation factor were not different during the dark phase and light phase. This is the first evidence of the steady state BNZ PK may not change according to the time of drug administration. Supported by CNPq, Capes, FAPEMIG and UFOP.
POPPK MODELING OF RESVERATROL ADMINISTERED TO WISTAR RATS

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Introduction: Resveratrol (RSV) is a polyphenolic antioxidant compound produced mostly by grapes under UV radiation. Interest in studying RSV has increased lately, mainly because its antioxidant activity. A better understanding regarding the pharmacokinetic (PK) properties of RSV is needed. So, this work aimed to perform a preclinical POPPK modeling of RSV.

Methods: After the administration of 5mg/kg via i.v. bolus and 50 mg/kg orally to animals (n = 6/group), plasma collection was performed at intervals up to 24 hours (CEUA/UFBA 048/16). The collected plasma was analyzed by HPLC/UV to quantify RSV. POPPK analysis was performed using the software Monolix® version 4.4.0. The parameters and micro-constants were estimated by calculating the maximum likelihood estimation of the parameters without linearization using the stochastic approximation expectation maximization algorithm combined with a Monte Carlo procedure.

Results and discussion: The final model was two compartment after both dosing tested. Typical Vc values were 5.2 and 20.5 L/kg for iv and oral dosing, respectively. The estimated micro-constants $k_{12}$ were 1.3 and 4.1 h$^{-1}$, $k_{21}$ were 0.5 and 0.6 h$^{-1}$ and $k_{10}$ were 0.3 and 0.4 h$^{-1}$ after i.v. and oral dosing, respectively. Typical ka was 2.4 h$^{-1}$. BSVs values were under 5%, indicating a good fit of the model.

Conclusions: The population pharmacokinetic evaluation after oral and intravenous administration showed that RSV presented the ideal model of two compartments with a longer exposure time in the body and greater distribution after oral administration when compared to the intravenous one.

ANTIOXIDANT CAPACITY AND STABILITY OF BANANA HEART TINCTURE (Musa spp.)

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Introduction: Banana, (Musa spp., family Musaceae), has proved to be a great food, with high potential for the pharmaceutical industry. Flavonoids, alkaloids, phenols, glycosides, terpenoids, saponins, carbohydrates, tryptophan are some of the substances found in rhizomes, pseudo-stem, leaves, flowers and fruits of banana tree. Therefore, the objective of this work was to evaluate the stability of a tincture produced with the heart of the banana bunch, through its antioxidant activity.

Methods: Following the protocol of the National Agency of Sanitary Surveillance (Anvisa), a tincture was made with 100g of the heart of the banana bunch and 120ml of cereal alcohol, being infused for 14 days. After that, samples were filtrated e divided in three subsamples: without storage, 30 days and 12 months of storage. All subsamples were analyzed by a method that evaluates the antioxidant capacity through the sequestering activity of the free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH). The reaction was performed by spectrophotometry at 515 nm, and monitored at 0, 15, 30, 45 and 60 minutes.

Results and discussion: The mean antioxidant activity of the initial tincture, without storage, was 59 %. In 30 days of storage, it was 34% and in 12 months was 31%. By presenting polyphenols and some reducing agents like thiols, bananas are rich in antioxidants, whose function is to inhibit the oxidation of other molecules, reducing free radicals and cellular oxidative damage.

Conclusion: The tincture with the heart of the banana bunch revealed high antioxidant content and its stability suffered little loss during the analyzed period.
DO SEX DIFFERENCES AFFECT THE BENZNIDAZOLE PHARMACOKINETICS IN DOG MODEL?

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Despite its toxicity and low efficacy during chronic phase, benznidazole (BNZ) is the drug of choice in Chagas disease (ChD). Scarce information about BNZ pharmacokinetics (PK) has been published. We previously reported the sex-related differences in BNZ-PK in healthy volunteers. The dog has been considered a good model to predict the ChD pathology and treatment efficacy. The aim of our study was to evaluate the effect of sex differences on the BNZ-PK in dog model. Eight healthy undefined breed dogs (n=4 males and 4 females in anestrus phase; mean weight=22kg) received a single oral dose of 3.5 mg/kg BNZ (LAFEPE, Brazil) on fed stomach (CEUA/UFOP:2016/37). Serial blood samples were collected for 48h following BNZ administration. BNZ serum concentrations were measured using HPLC-DAD. The one-compartmental PK parameters were calculated using Phoenix WinNonlin version 7.0 software and compared using the Mann-Whitney test (p ≤0.05). The oral PK parameters, $K_a$, $C_{max}$, $T_{max}$, $AUC_{0-\infty}$, Vd/F, CL/F and $K_{el}$, $t_{1/2e}$ showed remarkable consistency between female and male dogs. These results suggest that sex-related differences in $C_{max}$ and Vd/F of BNZ observed in healthy volunteers but not in dog model might be due to physiologic differences (i.e. gastric pH, rate of gastric emptying, gut transit time, intestinal expression of transport proteins and body composition). However, further studies using different phases of the bitch reproductive cycle will be needed to understand implications on the BNZ-PK in dog model and to discriminate between dog and human the mechanisms underlying differences.

Supported: by CNPq, Capes, FAPEMIG and UFOP.

ANALYSIS OF BENZNIDAZOLE IN DOG SERUM BY HPLC-DAD: APPLICATION TO A PRE-CLINICAL PHARMACOKINETIC STUDY

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Benznidazole (BNZ), the first-line drug to treat Chagas disease (ChD), has many limitations, including long treatment courses, several side effects and low efficacy during chronic phase. BNZ has been proposed to be eliminated mainly by CYP3A4 and P-glycoprotein (P-gp). This study describes the development and validation of a HPLC-DAD method for the determination of BNZ in serum, employing omeprazole as internal standard (IS). The biological samples (100μL) were desproteinized with acetonitrile (500μL) and the supernatants were analyzed by HPLC-DAD. Resolution of BNZ was performed in a RP-18 column using as the mobile phase a mixture of water:acetonitrile (65:35, v/v), eluting at an isocratic flow rate of 1mL/min, with a run time of 5 min. Detection of the BNZ and IS was achieved using DAD detector set at 324nm. The method was linear in the range of 0,1-100μg/mL for BNZ in dog serum. This method was applied to the pharmacokinetic (PK) study after the administration of intravenous single dose of BNZ (3,5 mg/kg) to eight healthy undefined breed dogs (CEUA/UFOP:2016/37). The BNZ PK parameters were: $C_{max}$ (μg/mL) = 8,11; $T_{max}$ (h) = 0,25; $AUC_{0-\infty}$ (μg.h/mL) = 90,54; $t_{1/2e}$ = 7,82; Vd/F (L) = 9,47; CL/F (L/h) = 0,91; $K_{el}$ (h⁻¹) = 0,09.

In conclusion, the method developed and validated exhibit confidence limits compatible with the application in a pre-clinical study on the BNZ PK in dog serum. Supported by CNPq, Capes, FAPEMIG and UFOP.
DRUGS USED TO TREAT DIABETES MELLITUS THAT DECREASE OVERWEIGHT

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Overweight and obesity have been growing significantly throughout the world, since physical exercise has been replaced by sedentarism coming from the new technologies, which are risk factors for type 2 diabetes mellitus (DM2). DM2 is characterized by hyperglycemia, inability to absorb glucose, associated with insulin resistance. The objective of this study is to review the drugs used in DM2 that help in weight loss. The study was carried out from a review of the scientific literature, using articles published between 2007 and 2017 in Portuguese, English and Spanish. The electronic databases used were: Scielo, ScholarGoogle, PubMed, VHL, CAPES. The descriptors and their crosses used were: “weight loss”, “α-glycosidase inhibitors”, “incretin analogs” and “biguanides”. According to research in the literature, the anti-diabetic pharmacological classes that reduce weight are: biguanides, α-glycosidase inhibitors and incretin mimics. Metformin is a biguanide indicated to treat DM2 in obese individuals. Inhibitors of α-glycosidase such as acarbose may aid in weight loss, in addition to minimizing weight gain through the use of sulfonylureas. Liraglutide (incretin analog) slows gastric emptying, increases satiety, decreasing appetite. Therefore, biguanides, α-glycosidase inhibitors and incretin mimics are pharmacological classes indicated as antidiabetics that aid in weight loss. However, it is essential to adhere to a low-calorie diet associated with correct pharmacotherapy and follow-up of the pharmacist.

TOXICITY OF SIROLIMUS INTRAVITREAL IMPLANTS IN NORMAL RABBIT EYES

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Introduction: Ocular inflammatory diseases, like uveitis, are one of the major causes of blindness worldwide. Over the past few years, SRL has become a topic of intense research in the ophthalmology community due to potent immunosuppressive, anti-tumor, antiinflammatory and anti-angiogenic properties. Despite its therapeutic potential, its clinical use is a major challenge. The evaluation of the toxicity caused by SRL administration through a drug delivery system is determinative for its safe use. The aim of this study was to determine both functional and morphological effects of the administration of SRL-loaded PLGA implants in rabbit retina. Methods: Group 1 received the PLGA implant and group 2 received the SRL-PLGA implant. Clinical evaluation of the eyes was performed weekly for 8 weeks after administration. Electroretinography (ERG) was recorded at baseline and after the injection. After the last electrophysiological assessment, the rabbits were euthanized and retinal histopathology was conducted. Results: No toxic effects of the implants or increase in the intraocular pressure were observed through clinical evaluation of the eye. ERG responses showed no significant difference between baseline and throughout the 8 weeks of follow up. No remarkable difference in retinal histopathology was detected in rabbit eyes. Discussion: The results from our study indicate that intravitreal SRL-PLGA implants did not cause functional changes in the retina of rabbits, which is confirmed by the clinical findings of indirect binocular ophthalmoscopy and histology. Conclusions: Our study suggests that PLGA-SRL implants are a promising alternative for the treatment of uveitis.

Acknowledgements: The authors acknowledge CNPq/MCT (Brazil), Fapemig (Brazil) and CAPES/MEC (Brazil) for the financial support.
ANNEXIN A1 CONTROL UTERUS LEUKOCYTE POPULATION BEFORE GESTATION

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Introduction: We showed that Balb/c mice genetically deficient in AnxA1 (AnxA1⁻/⁻) deliver more pups by litter than wild-type mice (WT). These effects were dependent on the female reproductive system since AnxA1⁻/⁻ mice presented increased blastocyst number and implantation sites. Pregnancy is a complex process, controlled by immune cells since fertilization until delivery. Therefore, here we characterize uterine leukocyte profile of non-pregnant WT and AnxA1⁻/⁻ mice. Methods: WT and AnxA1⁻/⁻ mice were euthanized by cervical dislocation after anesthesia and uteri were flushed with PBS/bovine serum albumin (BSA; 1%). The content was centrifuged, and cells were characterized as neutrophils (Ly6G⁺), T cells (CD3e⁺), macrophages (F4/80⁺), dendritic cells (CD11c⁺) and natural killer cells (NK1.1⁺). Data were acquired on a flow cytometer (Accuri C6; BD Biosciences) and 10,000 events were considered for analyses (CEUA protocol 521). Results: Equivalent number of neutrophils and NK cells were found in the uterus of WT and AnxA1⁻/⁻ mice. However, increased number of macrophage and T cells and reduced number of dendritic cells were found in uterus obtained from AnxA1⁻/⁻ mice. Conclusions: In summary, our data emphasize a role of AnxA1 in the uterus environment by showing that AnxA1 absence modifies uterus leukocyte population pattern. Alterations here observed may contribute to increased fertility previously observed in AnxA1⁻/⁻ mice. Additionally, AnxA1 may be emerging as a novel tool for fertility manipulation. Further investigations will complement our data.

Financial support: FAPESP 2014/07328-4, CAPES.

LASSBio1909, A NEW INHIBITOR OF HDAC6, PRESENTS ANTIDEPRESSANT-LIKE EFFECT IN CF-1 MICE

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Introduction: Diseases such as depression, anxiety and panic affect millions of people worldwide. Despite of pharmacological treatments available, disease recurrence is common, due to poor patient’s adhesion or drug ineffectiveness. In addition, the incomplete knowledge about the neurobiology of these disorders difficult the development of new drugs. Epigenetics studies aim to evaluate the influence of the environment on changes in gene function. The discovery of inhibitors of deacetylase enzymes brought a new insight into epigenetic studies, including studies on depression and anxiety disorders. Rodrigues and co-workers (J. Med. Chem. 2016, 59, 655-670) reported a series of new HDAC6 inhibitors, among them LASSBio-1909 and 1911. The aim of this study was to start the psychopharmacological pre-clinical evaluation of these compounds by testing them in the open field and tail suspension tests. Methods: Mice CF1 (male; 25 – 35 g) were treated with LASSBio-1909 and LASSBio-1911 (3 – 30 mMol/ kg), by oral and intraperitoneal routes, and evaluated in the open field (OFT) and tail suspension (TST). Results and discussion: LASSBio-1909 (10 mMol/kg) increased time spent in the OFT periphery zone, which suggest an anxiogenic-like effect. At 30 mMol/kg (p.o.) this compound presented an anti-immobility effect on TST, indicating an antidepressant-like effect. LASS-Bio-1911 was ineffective. Conclusion: LASSBio-1909 seems to present anxiogenic and antidepressant effects depending of the dose and route of administration. As it was active only by oral route, we may suggest that the activity is due to active metabolites. Ethical Approval: CEUA/UFRGS 33959 Financial Support: INCT-Inofar, CNPq and CAPES.
ULIGINOSIN B SHOWS TOXICITY IN CAENORHABDIS ELEGANS MODEL

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Introduction: Uliginosin B (ULI) is a dimeric phloroglucinol from Hypericum polyanthemum. Studies have shown the antidepressant-like effect of ULI in rodents. This effect seems to be related to inhibition of monoamines neuronal reuptake, especially dopamine (Stein et al., Behavioral Brain Research, v. 228, p. 66-73, 2012). These findings indicate uliginosin B as a molecular prototype to develop new antidepressants, and point out to the need to evaluate ULI safety and elucidate its site of action. In this study, we employed the Caenorhabditis elegans model to investigate safety and interaction of ULI with dopaminergic neurons.

Methods: C. elegans N2 and BY 200 (dopamine neuron marked with GFP) strains maintained on Nematode Growth Medium seeded with E. coli at 20°C. Worms were synchronized and treated at the first larval stage by age. ULI concentration ranged from 1 to 20 μM. CL₅₀ was determined by no-linear regression. The production of reactive species of oxygen (ROS) was measured by DCF-DA. Neuronal Fluorescence was observed by microscopy (Olympus IX-71) captured BY 200 images.

Results and discussion: The LC₅₀ of ULI was determined as 14 μM. ULI increased ROS in a dose (U-shaped curve, with effect at 1 and 20 μM) and time (at 60 min) dependent manner, and reduced dopaminergic fluorescence was observed in the BY 200 strain at 20 μM.

Conclusions: The effects of ULI on C. elegans N2 strain indicates high toxicity. The ability of ULI in reducing BY 200 fluorescence suggests that ULI decrease the activity of the dopamine transporter, which is in accordance with previous results.

Acknowledgements: PhD scholarship from CAPES.

PK-PD MODELING OF VORICONAZOLE AGAINST Candida albicans USING TIME-KILL CURVES AND SIMULATION

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Introduction: Although the minimal inhibitory concentration has been used as the most popular prediction tool for antifungal action, lately integrated into the PK/PD indexes, this pharmacodynamic parameter do not consider time-related antifungal effects, such as killing rate. Thus, the aim of this study was to propose a PK/PD modeling for voriconazole (VRC), against C. albicans (ATCC 10231) employing an in vitro infection model and simulate the clinical outcomes in different scenarios of doses. Methods: A one-compartment in vitro model was used to simulate free VRC tissue levels expected after oral administrations of 200 and 300 mg doses (q12h and q24h). An Emax model was used to model the curves (Scientist®). The Monte Carlo simulation (Berkley Madonna®) was done using the free levels expected in the renal of HIV patients after administration the same doses of VCZ for five week.

Results and discussion: A modify Emax-model was used to model the dynamic effect as a function of time. The PK/PD parameters were: EC₅₀ of 2.96±2.11 μg/mL and Kmₜₐx of 0.26±0.18 h⁻¹ for C. albicans. Simulating showed that for the smaller dose 10 % of patients respond to treatment and a time of four weeks is enough to eradicate the yeast. However comparing the treatment with the curves of growth controls the exposure to 400 mg of VCR demonstrates a difference in 2 log of CFU, demonstrating its fungistatic effect against C. albicans.

Conclusions: The PK/PD model tested adequately described VRC antifungal activity and can be used to compare and optimize drug regimens for this drug.
PERINATAL ENRICHMENT INDUCES ANXIOUS-LIKE BEHAVIOR AND IMPAIRS THE ANTIDEPRESSANT LIKE EFFECT OF BUPROPION IN CF1 MICE

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Introduction: The influence of environmental enrichment (EE) on pharmacological and behavioral responses in animal models of psychiatric diseases has not fully established yet. The aim of this study was to evaluate the effect of EE in different life periods on behavioral and pharmacological responses in open field (OFT) and forced swimming test (TST). Methods: Dams (CF1 mice) were exposed or not to EE from mating until offspring weaning. Pups were located to receive or not the EE, comprising four groups: NE - housed under standard condition; PE - housed under enriched conditions during perinatal period (from mating to PND21); LE - housed under enriched condition all their life (from mating to PND 58); PWE - housed under enriched conditions from weaning until PND 58. At PND58 mice were treated with vehicle (10mL/kg), bupropion (30mg/kg p.o.) or fluoxetine (30mg/kg p.o.) and evaluated in the OF and FST. Hippocampal BDNF was measured through PCR-RT. Results: PE group spent more time in OF peripheral zone, presented higher crossing and lower grooming than NE group. PWE and LE increased grooming behavior, and bupropion (LE) and fluoxetine (PWE) blocked this effect. All EE enrichment regimen abolished the anti-immobility effect of bupropion in the TST. None of the EE regimen affected mice hippocampal BDNF RNAm. Conclusion: environmental enrichment affected behavioral and pharmacological responses in the open field and forced swimming tests in a different manner depending of life period. Perinatal enrichment provokes anxiety in adulthood. The monoaminergic neurotransmission seems to play a role in these alterations.

Ethical approval: CEUA-UFRGS (31882).

Acknowledgments: CNPq, CAPES-PROEX and PRAE-UFRGS

ANALYSIS OF ALLOPURINOL AND OXYPURINOL IN DOGS URINE BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY WITH MASS-MASS DETECTOR (LC-MS/MS): A FOCUS IN VETERINARY PHARMACOKINETICS

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Introduction: Allopurinol is a potent inhibitor of the xanthine oxidase enzyme. In veterinary medicine allopurinol is indicated in the treatment of canine visceral leishmaniasis. Allopurinol is utilized to inhibit the synthesis of Leishmania RNA. The aim of this work is to develop and validate an analytical method for quantification of allopurinol and its active metabolite oxypurinol in dog urine using HPLC-MS/MS in order to perform pharmacokinetics analysis. Materials and Methods: The conditions defined for development of the chromatographic analysis of dog urine samples by utilizing the mobile phase of the HPLC-MS/MS consist of a mixture of 0.1% of formic acid (88%) and ammonium acetate 10mM. Allopurinol and oxypurinol were separated on a LiChrospher® 125-4 LiChrospher® 100 RP-8 (5 µm) column. Dog urine samples (25 µL) were extracted with acetonitrile. Acyclovir was utilized as an internal standard. The validation of the HPLC-MS/MS method was determined by limits of detection and quantification, linearity, stability, reproducibility and repeatability. Results and discussion: The method had a lower quantification limit of 10 µg.mL⁻¹ for both allopurinol and oxypurinol. The analysis was linear at concentrations of 10-1000 µg.mL⁻¹ for allopurinol and 10-200 µg.mL⁻¹ for oxypurinol. The precision value intracurrent and intercurrent for all concentrations presented had a coefficient variation lower than 15%. The confidence limits of HPLC-MS/MS for analysis of allopurinol and oxypurinol in dog urine indicates that the method is applicable to the multiple dose pharmacokinetic study of allopurinol in dogs with visceral leishmaniasis. Conclusions: It is efficient, accurate and sensitive study to Pharmacokinetic research.

Financial Support: CNPq.
RESPONSE TO CHOLESTEROL-LOWERING THERAPY IS ASSOCIATED WITH ADVERSE MUSCULAR EVENTS IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

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Introduction: Statins are the first-choice treatment for primary dyslipidemias, including familial hypercholesterolemia (FH), but the response is highly variable. The association of the response to cholesterol-lowering therapy with adverse events and adherence to therapy was investigated in a group of FH patients. Methods: Twenty-six FH patients diagnosed using MEDPED criteria were enrolled, and 18 had molecular diagnosis confirmed by mutations in LDLR, PCSK9 and APOB using next generation sequencing. Clinical, pharmacotherapy and statin-related adverse muscular events (AME) data were obtained from medical records and adherence to therapy was confirmed by interview. Therapy target was considered as 50% reduction in plasma low-density lipoprotein cholesterol (LDL-c) from baseline.

Results and discussion: Initial therapy included simvastatin (73.1%, 10-80 mg/d), atorvastatin (15.4%, 10-80 mg/d) or rosuvastatin (11.5%, 20 mg/d) in monotherapy or combined with ezetimibe (53.8%, 10mg/d). Pharmacotherapy did not differ between patients that reached or not the target therapy (TT) (p>0.05). TT patients had higher LDL-c reduction at high-intensity treatment (56.2%) than non-TT group (37.6%). Conclusions: In FH patients, the response to cholesterol-lowering therapy is associated with high dose treatment and increased risk for statin-related adverse muscular events.

Ethical approval: CAEE n.º 24618713.0.1001.5462 (Institute Dante Pazzanese of Cardiology) and CAEE n.º 24618713.0.3001.0067 (School of Pharmaceutical Sciences, University of Sao Paulo).

Financial support: FAPESP (#2016/12899-6) and CNPq (#447120/2014-0).

THE EFFECTS OF LIPOPOLYSACCHARIDE (LPS) INTRA-HIPPOCAMPAL INJECTION ON DIFFERENT BEHAVIORAL ANALYSES

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Introduction: Lipopolysaccharide (LPS) induces complex biochemical and behavioral alterations in experimental animals, causing learning and memory impairment. Therefore, LPS is used as a neuroinflammation model. The present study aimed to analyze the effects of LPS intra-hippocampal injection on different behavioral analyses. Methods: 30 male Wistar rats were allocated in three groups: SAL-IH, LPS-IH, and CT. Animals of LPS-IH and SAL-IH underwent a stereotaxic surgery in which 10 µg/ side of LPS (Sigma Chemical®) and saline, respectively, were injected bilaterally into the hippocampal CA1 region. CT group had not undergone surgery. After 30 days of recovery, three distinct mazes were utilized to analyze rats’ memory: Morris water maze, Radial maze, and object recognition task in open field maze. The present study was approved by the Institutional Ethics Committee on Animal Use (no. 029/2015). Results and discussion: A significant difference was found between LPS-IH and the other groups, in Morris water maze, Radial maze, and object recognition task in open field maze. The present study was approved by the Institutional Ethics Committee on Animal Use (no. 029/2015). Conclusion: The memory deficit promoted by intra-hippocampal injection of LPS was effectively assessed in Morris water maze and object recognition tasks, but not in Radial maze task.

Financial support and acknowledgments: The authors acknowledge CAPES (Brazil), as well as CNPq and Araucaria Foundation from Paraná state for financial support.
(Z)-N’-HYDROXY-4-METHYLBENZIMIDAMIDE: SYNTHETIC STUDY, STRUCTURAL CHARACTERIZATION AND TOXICOLOGICAL BIOASSAY AGAINST LARVAE OF ARTEMIA SALINA LEACH

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Introduction: Amidoximes have the general formula RC (≡ NOH) NH2, wherein R may be an alkyl or aryl group. These compounds belong to a class of compounds of undeniable relevance to pharmaceutical and technological industries, they are used as amidinic prodrugs and can be used as metal ion chelating agents in sea water. In addition, some amidoximide derivatives containing the carboxylic group have been patented to behave as potential therapeutic and prophylactic agents against cancer, Pneumocystis carinii pneumonia, among others. Amidoximes derivatives have pharmacological potential, which explains the need to know both the biological properties of the synthetic products and their respective toxic potential, so they can be applied safely. Due to the importance of these compounds, the present work aimed to synthesize and characterize (Z) -N’-hydroxy-4-methylbenzimidamide and later verify its toxicology in relation to A. Leaching Salina.

Method: A (Z) -N’-hydroxy-4-methylbenzimidamide was synthesized from the reaction between p-methylbenzonitrile and hydroxylamine hydrochloride in hydroethanolic medium, characterized by 1H and 13C NMR spectroscopic techniques, while the LC50 of arsenic was determined using POLO-PC software.

Results and discussion: (Z) -N’-Hydroxy-4-methylbenzimidamide was obtained in 89% yield as a crystalline solid, and the spectroscopic data obtained are in agreement with the literature. The toxicological bioassay with A. Saline Leach showed an LC50 of 35.474 μg / mL, which is a highly toxic value.

Conclusion: Given the above, the positive toxicological activity found can act as a pre-evaluation of substances with pharmacological potential and be used in studies of structural modification to be possible prodrugs.

PHYTOTHERAPY AND ANTIOXIDANT CAPACITY OF BANANEERS INFLORESCENCE MOTHER-TINCTURE (MUSA SPP.)

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Introduction: Phytotherapy is based on the use of plants as medicines. It uses parts of plants such as leaves, stems, roots, flowers and seeds with known pharmacological effect. Banana, (Musa spp., Family Musaceae), has great nutraceutical value and high levels of antioxidants. Therefore, the objective of this work was to evaluate the stability of a mother-tincture produced with the banana inflorescence, through its antioxidant activity. Methods: Following the protocol of the National Agency of Sanitary Surveillance (Anvisa), a mother-tincture was prepared with 100g of inflorescence and 120ml of cereal alcohol, being infused for 14 days. The sample was then filtered and stored in amber glass. Using the method that evaluates the antioxidant capacity through the sequestering activity of 2,2-diphenyl-1-picyrylhydrazyl (DPPH) free radical. The reaction was performed by spectrophotometry at 515 nm and monitored at 0, 15, 30, 45 and 60 minutes, right after filtration, at 30 days and at 12 months. Results and discussion: The average antioxidant activity of mother tincture was 59%. At 30 days of 34% and in 12 months it was 31%. When presenting polyphenols and some reducing agents like thiols, bananas are rich in antioxidants, whose function is to inhibit the oxidation of other molecules, reducing free radicals and cellular oxidative damage. Moreover, in its composition we find a sufficient amount of other biologically active substances that are documented in traditional and scientific literature making it a medicinal plant, with many pharmacological properties like antifungals, antioxidants, antiallergics, anti-inflammatory, regulator of the intestine, anticarcenogenic and hepatoprotectors. Conclusion: The mother-tincture with the inflorescence of the banana revealed a high antioxidant content and its stability suffered little loss during the analyzed period, in this way, the natural antioxidant property of this flower can be a good substitute for the synthetic, beyond contributing to the prevention of other diseases.
PLASMIN PROMOTES ANTI-ADHESIVE PROPERTIES IN FLOWING NEUTROPHILS WITHOUT MODIFYING FEATURES OF NEUTROPHILS OR CAUSING ENDOTHELIAL CELLS ACTIVATION

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Introduction: Plasmin (Pla) is the central protease of the fibrinolytic system, with actions on distinct cellular processes aside fibrinolysis. We have previously shown that the pharmacological treatment with Pla reduces neutrophil accumulation in the inflammatory site, which is linked to increased neutrophil apoptosis and efferocytosis. However, it remained unclear if Pla also interferes with neutrophil recruitment. Methods: Human neutrophils treated or not with Pla were flowed over a monolayer of human endothelial cells and neutrophil capture, adhesion, rolling and transmigration were quantified. The expression of adhesion molecules and Annexin A1 by resting or TNF-α-stimulated neutrophils was investigated. The impact of Pla on neutrophil function and reactivity was examined by measuring microvesicle release and the phagocytic activity of treated neutrophils. The effects of Pla on endothelial cell activation was investigated by flow cytometry and flow chamber assay. Results and discussion: Pla reduced adhesion and subsequent activation of neutrophils under flow, which was mirrored by an increased rate of rolling cells. These effects were not attributable to changes in surface adhesion molecules on neutrophils. Indeed, microvesicle generation, a marker of neutrophil activation, and phagocytosis of Escherichia coli remained unchanged after treatment. However, Pla induced a discrete increased expression of the pro-resolving protein Annexin A1. Finally, Pla did not induce activation of resting endothelial cells, nor prevented their cytokine-induced activation. Conclusions: We observed an inhibitory effect of Pla on neutrophil-endothelial cell interactions under flow, unrelated to cell activation or changes on adhesion molecules, but associated with an increased expression of AnxA1 by neutrophils. Financial support: CNPq; CAPES; CAPES-PDSE.

A NOVEL METHOD AND APPARATUS FOR DISSOLUTION ASSAYS USING DRY POWDER MICROPARTICLES

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Introduction: Dissolution assays in dry powders using gelatin capsules are carried out to predict drug profiles in different simulated media. In this context, there are several problems regarding this method, such as gelatin cross-linking and pellicle formation, demonstrating the need of novel approaches. Methods: Dry powder microparticles were produced by Spray-Drying micro-atomization (Mini Spray-Dryer B-290 (Buchi®) and compressed dry powder microparticles were obtained using a Texturometer (TA.XT plus Texture Analyzer - Stable Micro Systems®). A new apparatus was developed to determine dissolution profiles of these compressed dry powder microparticles in four different media, as well as the use of gelatin capsules to observe possible interactions. Results and discussion: Compressed microparticle formulations showed similar diameter, scanning electron microscopy images and drug recovery as compared to the non-compressed dry powder microparticles. For dissolution profile, contrasting with the poor results observed with the gelatin capsules, good reproducibility and repeatability were obtained for the proposed method and apparatus, which were submitted to the Brazilian Patent and Trademark Office (INPI) under number BR1020180090933. Conclusion: The method an apparatus showed to be simple, low cost and reproducible, allowing the characterization of dry powder dissolution profiles without gelatin capsules in four different media.
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