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Abstracts Book

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Heated tobacco vapor and cigarette smoke exposures: immunotoxic outcomes in T cell biology

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Non-combustible tobacco products arise worldwide as a potential harm reduction tool for current smokers. Heat-not-burn tobacco (HNBT) products are tobacco-based devices that allow tobacco to be heated but not burnt, releasing mainly nicotine and humectants, which leads to lower emission of toxic xenobiotics than cigarette smoke (CS). However, the toxicity of these devices remains unclear. Tobacco products are known to impair immune cell functions. T CD4+ cells are adaptive immune cells that differ into effector or regulatory cells due to their high phenotypic plasticity. An imbalance between effector and regulatory T CD4+ cells plays a pivotal role in autoimmune diseases, including rheumatoid arthritis and multiple sclerosis. Although CS is a well-known risk factor for autoimmune disease onset and progression, the impact of HNBT remains unclear. Herein, we investigated the effects of HNBT and CS exposures during the early or late T CD4+ cells activation markers and their outcomes on T CD4+ polarization and proliferation. T CD4+ cells were isolated from peripheral blood mononuclear cells collected from healthy donors using microbeads. Purified T CD4+ were exposed for 30min (2s of smoke/vapor followed by 28s of airflow) using peristaltic pumps. Cell viability was evaluated 24h after exposure by annexin V/7AAD labeling. T CD4+ were exposed and incubated with T cell activators. Mitochondrial and total reactive oxygen species were evaluated (mROS and ROS) for 1h, 24h (CD69, CD25), or 96h (proliferation and CD25/CTLA-4) after exposures. T CD4+ were incubated under Th17 or Treg polarization condition medium for 96h. Both exposures to HNBT and CS did not compromise the PBMCs' viability, however, only CS exposure increased the production of mROS and ROS, while both HNBT and CS decreased CD69 and CD25 activation markers 24h after exposures. HNBT impaired T CD4+ proliferation and late CD25 expression. Under polarization conditions, CS exposures increased Th17 frequency and RORγT transcription factor expression; and reduced Treg cells frequency. Although HNBT did not alter Th17/Treg balance, we observed that T CD4+ exposed cells display a higher expression of the anergy marker CTLA-4. Although HNBT does not favor a pro-inflammatory profile like CS, HNBT impairs cell proliferation, leading to a hyporesponsive phenotype. Our findings show that CS and HNBT exposures affect CD4+ T biology in different ways favoring an enhanced or impaired T cell response.

Immunosuppressive properties of mesenchymal stem cells spheroids versus monolayer culture: The impact of cell-cell contact

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Background: It has been proposed that the 3D culture of Mesenchymal Stem Cells (MSCs) may constitute a strategy to enhance their functional properties. Objective: Here, we constructed spheroids from adipose tissue-derived MSCs and investigated whether the 3D shape could enhance their immunosuppressive potential. Methods: Agarose-coated 96-well plates were used to generate MSCs spheroids, and the traditional monolayer culture was used for the two-dimensional (2D) model. The spheroid's diameter and morphology were analyzed by Scanning Electron Microscopy while MSCs phenotype, viability, adhesion molecules expression, and ability to control T-cell response were assessed by flow cytometry. Furthermore, we investigated the transcript levels of immunomodulatory genes using qPCR. Results: The spheroids generated presented a diameter of 257µm, a uniform shape, and a reduction in the expression of classic markers such as CD44 (p<0.0001), CD73(p<0.0001), CD90(p<0.0002), and, CD105 (p<0.0001) when compared to cells in 2D model. The spheroids also presented a slightly decreased in cell viability (p<0.001). Interestingly, although 3D culture upregulated the expression of anti-inflammatory genes such as TSG-6, IL-10, and TGF-B1, the 2D cultures exhibited a stronger capacity to suppress T-cell proliferation (p<0.0001), and a higher expression of ICAM-1 (p<0.0001) and VCAM-1(p<0.0001) when exposed to an inflammatory environment. Conclusions: Overall, our data showed that MSCs from adipose tissue were able to spontaneously form spheroids *in vitro*. Additionally, although the 3D culture method upregulated the expression of several immunomodulatory genes, the cells from 2D culture are still superior in suppressing T-cells proliferation, probably mediated by an increased expression of cell adhesion molecules. These results highlight that even though soluble factors are essential for MSCs immunoregulatory ability, the direct cell-to-cell communication mediated by surface molecules such as ICAM-1 and VCAM-1 may be helpful to attain maximum immunosuppression by MSCs.

Novel broad-spectrum virucidal HSPG-mimicking nanoparticles

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HSPG are negatively charged branched polysaccharides at the host cells' surface, which viruses widely use as binding receptors. Since the 60s, various sulfated and sulfonated compounds have been used as HSPG mimics to inhibit viral entry. However, the reversible nature of the virus inhibition mechanism has prevented the translation of these compounds to the clinic. We used a human endogenous organosulfonate bile acid to obtain non-toxic and virucidal nanoparticles. Therefore, this work aimed to develop safe and biocompatible nanoparticles with an HSPG-mimicking surface (NP) to damage viral particles irreversibly. NPs were produced by the ultrasonication technique and were physicochemical and morphologically characterized. Their stability upon nebulization and mucus interaction was verified using twin-impinger and artificial mucus. Toxicity was assessed by resazurin and LDH assays and cell uptake by cytometry and CLSM. NP mechanism of action was investigated by the time of addition experiments using HSV2 as a model virus. Inhibition studies were performed against HSV2 and wild-type SARSCoV2 by plaque assay. HSV2 binding assays were performed at 4oC and 37oC. The virucidal activity was proven by plaque assay, DNA release assay, and TEM. NP's antiviral activity was confirmed in a model close to an in vivo infection, using 3D histocultures of the upper respiratory tract against SARSCoV2. NP presented suitable features for pulmonary and vaginal administrations. NP exhibited stability upon nebulization, mucus-diffusibility, a CC50 of 1.9 mg/mL, and Vero cell uptake of 52%. The IC50 against HSV2 was 3.9 µM and 152.3 µM in the virus-pretreatment and post-infection treatment, respectively. NP competitively blocked infection of the virions attached to the cell membrane by 75%. NP exhibited a virucidal mechanism of action by damaging the HSV2 envelope. NP showed virucidal activity and IC50 against SARSCoV2 Δ and O variants of 486.3 µM and 205.1 µM, respectively. Using 3D tissues, the daily administration of NP reduced SARSCoV2 infection, 72 hpi, by 53% and 33% in the co-treatment and post-infection treatment assays. NP proved to be active against HSPG-dependent viruses, exhibiting broad-spectrum and virucidal mechanisms of action. We demonstrated their preventive and therapeutic activity in different cell lines and 3D respiratory tissues. Molecular dynamic simulations and in vivo studies will be perfomed for better mechanistic understanding and proof of concept.

Oral Presentations

(TS2) In silico drug-likeness and ADME properties prediction for ecto-5'-nucleotidase inhibitors

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Background: Ecto-5'-nucleotidase (ecto-5'-NT) accounts for the major production of adenosine (ADO) in the extracellular medium and it is overexpressed in several cancer cell lines. High levels of ADO act as immunosuppressor and it is related to neoangiogenesis, vasculogenesis and immune system evasion of neoplastic cell. Thus, the development of inhibitors of ecto-5'-NT may slow the cancer's growth and diminish the neoplastic cell evasion. Objectives: This work aims to predict the drug-likeness and ADME properties of 766 compounds screened by several groups in the literature using two freely available webservers in order to evaluate their main features. Methods: A total of 766 compounds reported at literature were firstly drawn and converted to SMILES and had their chemical class assigned as a label. Then, the drug-likeness and ADME properties were predicted using two open source webservers: SwissADME and pkCSM. A total of 82 descriptors were obtained and the features related to Lipinski (molecular weight, Moriguchi's logP, number of hydrogen bond donor and acceptors) and Veber filter, rotatable bonds and topological polar surface area (tPSA) were further evaluated through descriptive statistics. Furthermore, the predictions related to gastrointestinal absorption (GI absorption) and blood-brain barrier (BBB) permeability were evaluated towards their relative frequency. Results: The evaluation of the rules compliance indicates that most of the compounds were within the rules. Although, some chemical classes may display some issues regarding gastrointestinal absorption and blood-brain barrier permeability especially due to high log P (e.g. azole derivatives) and to high tPSA (e.g. nucleotide analogues). Conclusion: Most of the compounds screened at ecto-5'-NT followed Lipinski and Veber rules, although some classes may have difficulties towards absorption and BBB permeability. Acknowledgements: The authors thank to CNPq and CAPES for the financial support.

(TS3a) Preliminary stability of natural-based emulsion containing soursop seed oil (Annona muricata L.)

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Background: Enabling the use of natural ingredients to replace traditional synthetic ingredients is a challenge. The soursop seed oil (SSO) (Annona muricata L.) is a potential product for use in cosmetics because of its rich composition in fatty acids and acetogenins. Besides, the use of this vegetable oil allows to ensure sustainability by reducing waste and environmental impact, since the seeds are commonly discarded after processing the soursop fruit. Objectives: The main goal was to evaluate the physicochemical stability after the incorporation of SSO in a natural-based cream. Methods: Increasing SSO concentrations (2.5%, 5% and 10%) were added in creams, which were submitted to physical stress evaluation, by centrifugation (1000, 2500 e 3500 rpm, 15 minutes) and the thermal stress tests (40ºC to 60ºC, heating ramp of 10ºC, every 30 minutes). In each temperature cycle, samples were centrifuged at 2000 rpm, 10 minutes). The 2.5% SSO emulsion was subjected to preliminary stability study for 35 days, under the temperature of 40º ± 2ºC (laboratory oven) and under room temperature (15 to 30ºC), and characterized by physical aspect, pH and texture profile. Results: After physical stress, the emulsion containing SSO 2.5% was selected. The pH of the emulsions stored at room temperature remained in the range between 5.53 and 6.10, during 35 days of storage and there was no significant variation ($p > 0.05$) as well as the parameters elasticity, cohesiveness, adhesiveness, adhesion strength and hardness of emulsions stored in both conditions. All samples remained intact, without coalescence and with the same spreadability. Conclusions: It was developed a non-ionic oil-in-water emulsion containing SSO 2.5%, entirely composed by natural raw materials, resulting in a cream with a glossy and elegant appearance, pH in the range of 5.5-6.1, and suitable texture for skin application. The use of SSO as a raw material in the production of a moisturizing emulsion, provides innovation within the cosmetic segment and is an alternative to the overuse of ingredients potentially harmful to the environment. The potential use of SSO as a healing agent will be investigated.

(TS3b) Novel natural depigmenting active from the amazon region: cutite fruit extract (Pouteria macrophylla)

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BACKGROUND: The identification of novel actives for an effective treatment of cutaneous hyperchromias is a vast demand of the Cosmetics Industry, as existing compounds can trigger several adverse effects. The fruit of Pouteria macrophylla (Lam.) Eyma, popularly known as Cutite, is rich in gallic acid, an active that has demonstrated depigmenting activity in preliminary studies. OBJECTIVE: To verify for the first time the depigmentation action of cutite fruit extract (EXT) and incorporate it into a safe and effective topical microemulsion formulation (ME). METHODS: EXT effects on cell viability, melanin synthesis, and the expression of the melanin synthesis-related genes transcription factors were evaluated in melanocytes in vitro cell cultures (B16F10). A stable ME was developed and fully characterized. Safety was assured by a skin irritation test with reconstituted epidermis (Skin Ethic RHETM). After in vitro skin permeation, a tyrosinase bioassay assessed the formulation's ability to deliver the actives. The depigmenting effect of the final formulation was attested using 3D pigmented skin culture model. RESULTS: The melanocytes treated with the EXT presented a reduction of 32% and 50% of intra and extracellular melanin content, respectively, and strong suppression of melanin synthesis-related gene transcription factors. The microemulsion showed twice the tyrosinase inhibition of a conventional control emulsion (20.7 ± 2.2% and 10.7 ± 2.4%, respectively) following skin permeation in vitro. Histological analysis following the treatment of 3D pigmented skin showed a more pronounced effect of the developed ME containing the EXT in lightening and reducing the number of melanin spots than the positive control (a commercial depigmenting formulation containing kojic acid, one of the most used depigmenting compounds). CONCLUSIONS: This study identified a promising novel depigmenting natural extract from a fruit of the Amazon region. When incorporated in a microemulsion, the Cutite fruit extract showed remarkable depigmenting potential compared to a commercial depigmenting formulation.

(TS4a) Improved in vitro cytotoxicity and safety of multiple nanoemulsions co-encapsulating 5-fluorouracil and short chain triglycerides to treat colorectal cancer cells

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Colorectal cancer (CRC) is the third most common cancer in the world and fourth in cause of death world-wide. The drug of first choice is 5-fluorouracil (5FU), but due its low oral bioavailability and short plasma half-life, it is administered intravenously at high dosage and frequency which, combined with poor selectivity for tumor cells, leads to serious systemic adverse effects and limits the patient quality of life. We propose the co-encapsulation of 5FU with either tributyrin or tripropionin (short-chain triglycerides, SCT) in a multiple nanoemulsion (MN) of oral administration to enhance cytotoxicity and reduce the dose of 5FU necessary for treatment of CRC. Microemulsions w/o containing SCT in the oil phase and 5FU in the water phase were dispersed in an external water phase to form MN. Then we evaluated their cytotoxicity in CRC cell lines monolayer and spheroid, and safety in *Galleria mellonella* model. MNs displayed droplets of 400 nm and PDI of 0.2. The cytotoxicity assay in cell line monolayer HCT-116 wt, a KRAS mutated line, showed the incorporation of 5FU in MN without SCT led to a reduction of IC50 compared to its solution (4.6 to 2.7 μM, respectively). Inclusion of the SCT pronounced the reduction of IC50 (1.8 and 1.5 μM for tributyrin and tripropionin, respectively). HCT-116 TP53-null displayed less cytotoxicity to 5FU solution (IC50 = 15.8 μM) and incorporated in MN (IC50 = 8.2 μM). Addition of tributyrin, but not tripropionin, reduced the IC50 to 0.4 μM. HT-29, a TP53 and BRAF mutated line, showed higher resistance to 5FU solution (IC50 = 47.2 μM), but the incorporation improved the cytotoxicity in almost 10 times (IC50 = 4.9 μM). SCT incorporation did not improved cytotoxicity. The cell line CCD-18Co, a non-tumor colon cell, demonstrated higher IC50 values when treated with MN with 5FU (17.1 and 26.9 μM for tributyrin and tripropionin, respectively) compared to cancerous cell lines, suggesting selectivity. HCT-116 wt spheroids demonstrated high resistance to 5FU solution (40.9 and 34.6 μM for 48h and 72h respectively). When 5FU was incorporated into MN, the IC50 reduced in half in 48h and in third in 72h independently of SCT. Regarding safety, *G. mellonella* larvae survival rate was 100% after 5 days of treatment with MN with 5FU and SCT. These results demonstrated that co-encapsulation of 5FU with SCT in multiple nanoemulsions may potentiate the cytotoxic effects of 5FU, with relative selectivity for cancerous cells and great safety.

(TS4b) Conjugated-polymeric nanocapsules loaded with drug combination for targeting hepatocellular carcinoma cells

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Background: Hepatocellular Carcinoma (HCC) conventional chemotherapy has low selectivity and several side effects and poor prognosis, requiring new therapeutic approaches, such as active vectorization and drug combinations to improve chemotherapy. Eugenol (EG) rich oils have aroused interest due to their anti-inflammatory, antioxidant and antitumor properties. They can be combined with nitro-imidazoles (NI) in a repurposing approach, due to their oxi-reductive properties in hypoxic tumor conditions. Objective: The present work aimed at developing polymeric nanocapsules (NC) from PLA derivatives conjugated with carbohydrates to co-encapsulate NI and EG for active targeting of tumor hepatocytes in vitro. Results: NC co-encapsulated EG and NI with entrapment efficiency of 98% and 91%, respectively, mean size of 180 nm, -39.1 mV zeta potential. The in vitro activity against the human HCC cell line (HepG2), showed that NC presented higher cytotoxicity (IC50 11.95 µM and 22.41 mM NI and EG, respectively) when compared with the free solution of NI. NI, under hypoxic conditions, was able to increase ROS levels, confirming our initial hypothesis. Cellular uptake of NC, quantified by flow cytometry and fluorescence microscopy, showed that carbohydrate covalently bound to the surface of NC promoted greater internalization due to the interaction of the ligand and overexpressed receptors present in tumor hepatocytes. Conclusion: The active co-encapsulation of NI and EG in targeted polymeric NC decorated with covalently linked ligand has the potential to be evaluated in vivo in HCC models, as a promising candidate for "add-on" therapy for this cancer.

(TS5) Determination of matrix effect in Cannabis sativa products

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Background: In the last two decades, *Cannabis sativa* has gone from a forbidden substance worldwide to one that is gaining cultural and legal acceptance in many countries for medicinal and recreational use. As jurisdictions legalize cannabis products, increase the variety and complexity of these products that surpass dry plants material. That's why appropriate methods to quantify biologically active constituents are being developed to ensure safety and regulatory compliance. The main cannabinoids of regulatory and security concern are Δ9-tetrahidrocanabinol (THC), canabidiol (CBD), their respective acid forms THCA-A and CBDA and the canabinol (CBN). Sensitive and selective method for simultaneous analysis of these cannabinoids in plant material and oil are necessary. Objectives: The objective of this work is to determinate the matrix effect of dried plant material and oil for the analysis of THC, THCA, CBD, CBDA, CBN and CBNA using ultra performance liquid chromatography coupled with tandem mass spectrometry. Method: *Humulus lupulus* was and a mix of sunflower, coconut and extra virgin olive oils were used a blank plant and oil matrix, respectively. The blank samples were fortified with the cannabinoid analytical standards. Plant sample 100 mg was extracted with 5 mL acetonitrile: methanol (8:2), followed by centrifugation 1000 rpm for 10 minutes (Wang *et al*., 2018). Oil sample was just used diluted in acetonitrile. For all preparations were diluted in reason 1:100000 before injecting in the LC-MS/MS (API 3200, Sciex). Matrix effects were measured by comparing the peak area of the fortified blank matrix with standards in solvents. Results: Significant matrix was observed in plant matrix material and oil matrix, with an enhancing effect particularly obvious at low concentrations. The matrix effects were more pronounced in plant materials: THC (-22% to 14.8%), THCA (-16% to 14.3%), CBD (-3.7% to 23.7%), CBDA (1.3% to 134%), CBN (-71.6 to 287%) and CBNA (-17% to 78%) compared to the oil matrix: (C-(1-3% to 64.6%), CBDA (-50.6% to 24%), CBN (-1.79 to 27.9%) and CBNA (-42% to 85.5%). Conclusions: Although the extraction procedure involved a large dilution, it was not effective to eliminate matrix effects in both matrices. However, the use of deuterated standards as internal standards could compensate for this effect and eliminate the need to use in-matrix standard curve. Acknowledgments: Decanato de Pós-graduação (DPG).

(TS6) Frequency of T, B and NK cells in patients with chikungunya: what is the clinical value of immunophenotyping?

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Chikungunya virus (CHIKV), belonging to the genus Alphaviridae and the family Togaviridae, is transmitted by mosquito vectors of the genus Aedes sp., leading to a disease characterized mainly by high fever, headache, myalgia, rash, and joint pain. It is known that several cells of the innate and adaptive immune system act in order to promote viral elimination and return to the individual's homeostasis, including T, B and Natural Killers (NK) cells. Thus, the objective of this study was to characterize the immunophenotypic profile of T, B, and NK cells in the peripheral blood of patients with Chikungunya (CHIK), in the acute and subacute stages, evaluating their clinical associations and their possible use as indicators of chronification. To this end, at first, peripheral blood samples from controls (n=72), acute (n=55) and subacute (n=86) patients were collected and evaluated by flow cytometry in order to characterize the cells (TCD3+, TCD4+, TCD8+, BCD19+, NK (CD56+CD16+) and NKT (CD56+CD3+). Thus, it was possible to see a significant decrease in the frequency of TCD3+, TCD8+ and NKT cells, and a significant increase in TCD4+ and BCD19+ cells in patients with CHIK compared to the control group. Comparing the acute with the subacute cases, a significant increase in NK, NKT (CD56+CD3+), and TCD4+ cells and a decrease in TCD8+ and BCD19 were observed. After 90 days, the patients were evaluated for some symptoms and clinical parameters (rheumatological pain, fatigue, Global health assessment (AGS), painful and swollen joint count) to access their chronification status. Patients who became chronic (N=83) had their cell frequency associated with symptoms and clinical parameters. So, it was seen a positive association between TCD3+ cells frequency and the presence of rheumatologic pain. Also, there was an association between BCD19+ cells and fatigue as well as BCD19+ cells and AGS (p<0.05). For the painful joint count, was seen a positive correlation with the frequency of BCD19+ cells and NKT (CD56+CD3+) cells. Regarding swollen joints, there was no statistically significant difference for any cell. Therefore, T, B, and NK cell immunophenotyping contribute as a tool to identify possible predictors of the Chikungunya chronification process. Keywords: CHIKV; chronification; T, B, and NK cells.

(TS7a) Chemical composition, antimicrobial activity and synergism of essential oil from Croton conduplicatus (Euphorbiaceae) against Staphylococcus aureus

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Background: Croton conduplicatus is an endemic plant species, belonging to Euphorbiaceae family, distributed in some regions of Northeast Brazil. It is used to treat headaches, grippe, stomach pains and indigestion. Objectives: This study aimed to extract and identify chemical compounds present in C. conduplicatus essential oil (EO) and to evaluate the antimicrobial activity (AA) of EO and the effect of the EO associations with ampicillin (AMP) and oxacillin (OXA) against Staphylococcus aureus. Methods: The leaves were collected in city of Irecê, Bahia. Then, they were dehydrated in an air circulation oven for 72 h (40 ºC) and subjected to spraying in a mill, providing 704.2 g of plant drug (PD). After that, PD was submitted to hydrodistillation process using Clevenger apparatus for 3h and EO obtained was analyzed by gas chromatography/mass spectrometry (GC-MS). Minimum inhibitory and bactericidal/fungicidal concentration (MIC/MBC-MFC) of EO were determined against ATCC strains: S. aureus 25923 and 33591 (MRSA), E. coli 25922, P. aeruginosa 27853 and C. albicans 10231. The associations effects of OE-OXA and OE-AMP were determined by checkerboard method and interpreted by calculating the Fractional Inhibitory Concentration index (FICi), with synergistic effect FICi ≤ 0.5, indifferent 0.5 ≤ FICi ≤ 4.0 and antagonistic FICi ≥ 4.0. Results: 2.2 mL of EO were obtained and showed a yellowish color and characteristic odor. In GC-MS analyses, 71 compounds were identified, the majority being: eucalyptol, p-cymene, α-pinene, α-phelandrene and spathulenol. EO showed activity only against two strains of S. aureus with MIC values of 256-512 µg mL-1 and MBC of 512-1024 µg mL-1. All tested associations were synergistic with CIFi from 0.094 to 0.312. The associations reduced the MIC of EO and antibiotics by ≥ 87.5% and modified the resistance profile of S. aureus ATCC 33591 to oxacillin and ampicillin. Conclusions: C. conduplicatus EO has activity against S. aureus and when associated with oxacillin and ampicillin, it has a synergistic effect against methicillin resistant and sensitive S. aureus.

(TS7b) Chitosan-based film for transdermal delivery of naringenin

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Background: Naringenin is a bioflavonoid mainly found in citrus fruits. It presents many pharmacological benefits, including a remarkable anti-inflammatory activity, but its oral bioavailability is poor. To overcome this drawback, a transdermal administration of such bioflavonoid could improve therapeutic potential for treatment of chronic inflammatory conditions. Objective: The aim of this work was to develop a chitosan-based film with naringenin that guarantees a consistent transdermal drug delivery. Methods: First, naringenin's *in vitro* anti-inflammatory effect on T-cell proliferation was evaluated, followed by research on the modulation of gene expression for inflammatory factors in peripheral blood mononuclear cells. Chitosan films were then prepared and characterized. Afterward, naringenin release profile and drug permeation across porcine skin provided by a selected film were determined. Results: Naringenin induced the expression of the anti-inflammatory factors IL-10 and TGF-β1 (10.0 µg/mL, p<0.05) while inhibited the expression of the pro-inflammatory cytokine IL-1β and limited T-cell proliferation (1.0 and 10.0 µg/mL, respectively; p<0.05). Chitosan film was successfully developed and demonstrated suitable characteristics, as homogeneity in content (CV<2%). Naringenin was progressively released to the physiological media following both first order (R^2 = 0.97) and Korsmeyer-Peppas (R^2 = 0.91) kinetics. When topically applied, the chitosan film could stimulate a constant and continuous diffusion of drug across the skin over 72 h. Indeed, the permeation flux of naringenin was 0.30 ± 0.01 µg/cm²/h, which means a concentration in the receptor solution 14-fold (p<0.05) higher than that provided by the drug solution used as a control. Conclusion: The chitosan film represents a promising transdermal alternative for the long-term treatment of inflammatory conditions using naringenin.

(TS8a) Molecular modifications on basic group and aromatic moiety revealed important information of structure-affinity relationship for LINS01 compounds

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Background: In the last years our group had explored the 1-[(2,3-dihydro-1-benzofuran-2-yl)methyl]piperazines (LINS01 series) as histamine H3 and H4 receptor (H3R/H4R) ligands designed based on the JNJ-7777120 compound, an indolecarboxamide-piperazine with nanomolar H4R ligand. Objective: In order to eliminate the chirality and get information regarding the piperazine moiety as a basic group in these compounds, modifications were performed to increase the structure-affinity relationship data. Methods: A set of 10 compounds were designed by performing ring modifications, homologation and simplification strategies, and synthesized therefore. These compounds were assessed through binding assays at the H3R and H4R. Results: The compounds showed notable preference towards the H3R with binding affinities in micromolar and submicromolar range (pKi = 5.0-7.0). Only two homopiperazine compounds (LINS01h017 and LINS01h018) exhibited improved (but still low) affinity to the H4R (pKi ~5.2) than their piperazine counterparts. The aromatization of the dihydrofuran moiety to remove chirality led to compounds with comparable but lower affinity in some cases. Interestingly, the homopiperazine analogues (LINS01h) showed slightly improved affinities, as well as the ethylenediamine (LINS01e) counterparts. The replacement of the dihydrofuran to anilide led to compounds with lower affinity (pKi ~5.3), denoting the importance of this motif to the affinity of LINS01 compounds. Compound LINS01h007 should be highlighted in this series regarding its high affinity to the H3R (pKi = 7.02), although its affinity to the H4R (pKi < 5.00) was decreased in comparison to its homologue LINS01007 (pKi = 6.07). Conclusion: The results added important information for further development of H3R/H4R ligands.

(TS8b) LaSOM 335: a safe and active dihydropyrimidinone against bladder cancer cells

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Background: Bladder cancer is the fourth most common malignancy in men. It can present from mild to well-differentiated disease to extremely malignant tumors with low survival rates. The class of dihydropyrimidinones (DHPMs) became important as prototypes with antitumor activity due to the study of the biological activities. Objectives: evaluate *in vitro* antitumor activity on T24 bladder cancer cells and *in vivo* toxicity on *Caenorhabditis elegans* of LaSOM 335. Methods: Human bladder cancer cell line (T24) was cultivated in RPMI, supplemented with 10% fetal bovine serum (FBS) containing penicillin/streptomycin 0.5 U/mL. Cells were kept in a humidified atmosphere with 5% CO2 at 37ºC. Cells were seeded in a density of 10,000 cells per well in 96 well plates. After 24h, the medium was aspirated, and cells incubated with compounds dissolved in culture medium or dimethyl sulfoxide (DMSO) in 5, 10, 15, and 20 µM. For negative control culture medium or DMSO was used. Cell viability was evaluated by MTT. To verify whether the compound causes potential toxicity, we exposed N2 worms as above described and 48 hours after the treatment we scored the live worms. Three experiments were performed individually in duplicates. Results: the cytotoxic effects of LaSOM 335 were assessed on T24 urinary bladder cancer cell line using MTT assay after treatment for 24 hours. The results show a strong inhibition of cell growth for LaSOM 335 which displayed an IC50 of (10.73 ± 0.53 µM). The survival rate is one of the initial parameters for the toxicity assessment in studies using *C. elegans*. The results showed that LaSOM 335 significantly reduced the survival of N2 worms only when exposed to 600 µM proving to be relatively safe in the in vivo model of *C. elegans*. Conclusion: LaSOM 335 is a promising compound for further investigation in the bladder cancer field.

(TS9a) Ex vivo ocular model for performance evaluation of ophthalmic drug products: "whole eye globe" with simulated lacrimal flow

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Background: The cornea is a vital absorption route and a target for drug delivery. The excised cornea or animal models are currently used in the research and development of ophthalmic drug products. Nevertheless, all these models present limitations in simulating natural physiological conditions, either for their lack of dynamic protection mechanisms (such as lacrimal drainage) or for the anatomical differences from the human eye. Therefore, developing alternative ophthalmic models that evaluate drug penetration in the cornea while applying dynamic "protection barriers" is a contemporary challenge. Objective: To develop an alternative dynamic ex vivo model using porcine eye with a simulated lacrimal flow to evaluate the performance of pharmaceutical drug products. Methodology: Porcine eye globes were mounted on a support with custom-made donor media containing an inlet and an outlet designed to promote a simulated tear flow. A commercial rotary perfusion pump has integrated the system for the proper flow of simulated tear fluid (the system operated at 48 µL/min flow during the first 2 minutes followed by 33 µL/min flow until 15 minutes of experiment; donor compartment filled with 300 µL of formulation). The system was challenged by different formulations with different viscosities and mucoadhesive properties (solution; poloxamer gels (PLX) at 14, 16, and 20% and 16% PLX gel with chitosan (CS) at 0.5, 1.0, and 1.25%). Results were compared to the conventional excised tissue model mounted in modified Franz-type diffusion cells. Results: The "Whole Eye Globe" model with simulated tear flow was capable of differentiating formulations that contained a mucoadhesive component (CS) from those that did not (only PLX) in terms of drug amount that penetrated the cornea (p<0.05). The conventional excised tissue static model was not only unable to differentiate these formulations (p>0.05) but also resulted in about 5-fold the amount of drug penetrated in samples that lacked the mucoadhesive component, hence, overestimating the formulation performance. Conclusions: The "Whole Eye Globe" model with simulated tear flow is a promising new alternative method for performance evaluation of ophthalmic drug products.

(TS10) miR-183-5p as a target gene in prostate cancer: importance in therapeutic strategy

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Background: MicroRNAs (miRNAs) are small non-coding RNAs responsible for regulating gene expression through mRNA regulation. MiRNAs play important roles in physiological processes as cell proliferation, apoptosis and differentiation. Aberrant expression of miRNAs has been associated with prostate cancer (PC) development and progression, which may act as an oncogene or tumor suppressor. Therefore, miRNAs have been shown to be of great value for cancer diagnosis, prognosis and therapy. Thus, it is widely interesting to identify miRNAs molecular targets to understand their role in development and PC progression as well as their potential as a therapeutic target. Objective: Identify and confirm miR-183-5p molecular target in the PC cell line PC-3. Methods: Initially, the miRNA expression profile in the human PC cell lines PC-3 and LNCaP and human prostate epithelial cell line RWPE-1 were determined by microarray and the differential expression was confirmed by qPCR. miR-183-5p was chosen to be studied given the fold change (FC) and P values. To predict a potential target gene of miR-183-5p three bioinformatics tools were used: LinkedOmics, miRWalk v. 2.0 and Gene Ontology Resource. Therefore, to confirm in vitro a miR-183-5p target gene, transient transfection with miR-183-5p mimic and an inhibitor into PC-3 cells was performed and the target gene expression was analyzed by qPCR and western blotting. Results: The miR-183-5p was differential expressed between the cell lines and was significantly higher expressed in PC cells (LNCaP and PC-3) compared with non-tumoral RWPE-1 cells. By the bioinformatic analysis, TIMP3 was selected as a potential target gene of miR-183-5p in PC. Thus, the miR-183-5p downregulation significantly enhanced TIMP3 mRNA and protein expression in PC-3 cells. Additionally, the expression of MMP-3 and MMP-9, metalloproteinases regulated by TIMP3, was significantly inhibited when the TIMP3 expression was recovered. Conclusion: The present study demonstrated that TIMP3 expression is modulated by miR-183-5p on PC cells and that TIMP3 expression downregulates MMP-3 and MMP-9 expression. In this way, miR-183-5p demonstrated to be a potential target for novel therapy to prostate cancer.

(TS11a) Larvicidal activity and phytotoxicity evaluation of ivermectin encapsulated into polymer nanocapsules

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Background: The use of larvicides is an efficient strategy for vector control, particularly against *Aedes aegypti*. Recent research exploring the effects of well-known antiparasitic drug ivermectin (IVM) in *Aedes aegypti* larvae has proved lethal activity. However, IVM presents limitations such as poor water solubility, and toxicity for non-target species. Polymeric nanoparticles (PNs) are smart drug delivery systems able to control release, decrease toxicity and promote better efficacy. Objectives: This study sought to investigate the feasibility to encapsulate IVM in polymer nanoparticles (NP-IVM) intended for vector control. Particularly, we evaluated the activity of NP-IVM against *Aedes aegypti* larvae. Methods: Poly(ε-caprolactone) (PCL) nanocapsules loaded with IVM were prepared by nanoprecipitation method, and characterized in terms of size, morphology, charge surface, and encapsulation efficiency. The larvicidal assays used *Aedes aegypti* larvae stage 3, (Rockefeller strain) exposed to NP-IVM or free IVM (Tween 80, 3%) at concentrations (ppm) of 0.010, 0.050, 0.100, 0.150, and 0.250. Temephos (0.003 mg/L) was used as a positive control. Data were evaluated using the Probit method to determine lethal concentrations of 50% (LC 50) and 90% (LC 90). In another set of experiments, phytotoxicity assays were performed with *Cucumis sativus* in the same concentrations. Results: Nanocapsules exhibited size around 400 nm, negative charge and spherical morphology. Encapsulation efficiency of IVM reached 98%-100%. In *Aedes aegypti* larvae, NP-IVM showed a toxic effect at 0.05 ppm, resulting in LC 50 =0.077 ppm and LC 90 =1.147 ppm. Empty PN or free IVM did not show toxic effects even in any concentration used in the larvicidal assays. Both empty and IVM nanocapsules exhibited no toxicity against *Cucumis sativus*. Conclusions: See all together, these findings demonstrate the feasibility of using encapsulated IVM as a novel formulation strategy for vector control, warranting further research for exploring the role of nanomaterials against *Aedes aegypti*.

Keywords: larvicidal; phytotoxicity; ivermectin; nanoparticles.

(TS11b) Hyaluronic acid-conjugated liposomes loaded with dexamethasone: a promising approach for the treatment of inflammatory lung diseases

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Backgroud: Alveolar macrophages are the first immune cells that encounter incoming pathogens in the lungs. As such, they play a key role in the initiation and resolution of the immune response. Similar to other tissues, studies have highlighted the existence within the lung of a classically activated alveolar macrophages phenotype denominated M1 macrophages. These M1 polarized alveolar macrophages exhibit a pro-inflammatory profile and are known to mediate resistance towards intracellular parasites (i.e. bacteria, protozoa and viruses) as well as antitumor immunity. This makes them an interesting target for the treatment of inflammatory and infectious pulmonary diseases. Objectives: To obtain a formulation that could be easily applied in the clinic, three different Dexamethasone (Dex) loaded Poly(ethylene glycol) and/or Hyaluronic Acid-coated liposomes platforms (Lip-PEG-Dex, Lip-PEG-HA-Dex and Lip-HA-Dex) were developed and characterized. Methods: An inflammatory model to compare the affinity toward M1 polarized alveolar macrophages was developed in vitro and in vivo. M1 was stimulated with interferon-γ (INF-γ) and lipopolysaccharide (LPS) for 24 hours and their shape, granulometry as well as expression of key inflammatory markers such as CD86, iNOS and Tumor necrosis factor alpha (TNF-α) were evaluated by flow cytometry and ELISA Also, a spin label approach was used to investigate the dynamic of the lipid platforms. Results: In the inflammatory process, it was possible to observe an increase in CD44 expression and, consequently, a greater internalization of HA-liposomes. This shows the efficiency of hyaluronic acid receptors recognition both in vitro and in the BAL fluid in vivo. In the lung, HA-liposomes showed a reduction in macrophage targeting. This could be explained by the presence of two forces exercising a balance between mucus penetration and receptor targeting. Additionally, results showed a decrease in the production of the inflammatory cytokine TNF-α following treatment with drug loaded liposomes, when compared to free dexamethasone. The surface modifications did not induce any molecular changes in the membrane core of the liposomes. Our results indicate the benefits of encapsulating this drug into lipid nanoparticles designed to cross the pulmonary mucus layer. Conclusions: The three nano-lipids platforms were capable of recognizing M1-alveolar macrophages and treat inflammatory lung diseases.

(TS12) Drug reaction with eosinophilia and systemic symptoms associated with antibiotics: analysis of Brazilian Pharmacovigilance Records

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Background: Antibiotics can induce a rare syndrome known as DRESS (Drug reaction with eosinophilia and systemic symptoms). It is a serious condition characterized by the presence of eosinophilia and an acute skin rash, which has been poorly studied in the Brazilian context. Objectives: To assess the association between DRESS and antibiotic use employing pharmacovigilance data from the National Health Surveillance Agency (ANVISA, Brazil). Methods: This is an analysis of the reports available in the adverse drug event reporting system (VigMed) carried out between December 1, 2018 to May 08, 2022. The Medical Dictionary for Regulatory Activities (MedDRA) was used to identify cases of DRESS, the Anatomical Therapeutic Chemical (ATC) to distinguish antibiotic reports and International Nonproprietary Names (INN) to differentiate selected antibiotics. The Reporting Odds Ratio (ROR) with respective 95% confidence intervals (95% CI) was calculated to investigate the association between antibiotics and DRESS. Results: A total of 114,454 reports were considered, with 95 suspected cases of DRESS. Antibiotics (12,231 reports) had the highest proportion of DRESS, representing 3.8 cases/thousand reports. When compared to other drug classes, the occurrence of DRESS was statistically significant among any antibiotic (ROR=7.9; 95% CI: 5.1-12.0), meropenem (ROR=20.1; 95% CI: 10.2-36.5), vancomycin (ROR=19.4; 95% CI: 11.5-31.7) and cefepime (ROR=11,0 95% CI: 2.2-33.5). On the other hand, statistical significance was not found between DRESS and ceftriaxone (ROR=3.1; 95% CI:0,1-9.3) and with the piperacillin+tazobactam combination (ROR=2.9; 95% CI:0.3-10.7). Conclusions: The association between the reports of DRESS associated with antibiotics was evidenced, with special emphasis on drugs routinely used in the hospital context, such as meropenem, vancomycin and cefepime. It should be emphasized that this database has suspected adverse reactions, with no causality attributed, which means that medical events reported have been observed following the use of a medicine, but which are not necessarily related to or caused by the medicine.

(TS13) Induction of trained immunity by Covid-19 vaccination

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Background: Trained immunity has been described as the adaptation of the innate immune response induced by previous contact with some infectious agents or vaccines. The BCG, influenza and yellow fever vaccines were described as capable to induce innate memory phenotype in monocytes and NK cells, characterized by increased production of pro-inflammatory cytokines, altered immunometabolism towards glycolysis and epigenetics changes. Here, we hypothesized that vaccination against SARS-COV2 could induce training of monocytes. Objective: To investigate if monocytes from individuals completely immunized with two doses of CoronaVac or AstraZeneca/Fiocruz vaccines exhibit the phenotype of trained immunity. Methods: Peripheral blood derived monocytes were isolated from healthy unvaccinated or fully vaccinated individuals between 15 to 150 days after the second dose. To evaluate the training phenotype, monocytes were stimulated with LPS by 6 hours and the cytokines (TNF-α, IL-6, IL-1β and IL-10) production was accessed on the culture supernatant by ELISA. Cell surface markers were evaluated by flow cytometer and immunometabolic gene expression (LDHA, GLUT1, HK2) by qPCR. Results and Conclusions: After LPS stimulation, monocytes from vaccinated subjects express more CD163 than unvaccinated, a surface marker that suggests trained phenotype when associated with inflammatory conditions. However, monocytes from vaccinated individuals produced less TNF-α compared to unvaccinated individuals and monocytes from CoronaVac vaccinated subjects produced less IL-6 compared to unvaccinated subjects. Also, there were no differences between the groups on the surface markers HLA-DR and CD86 expression. The expression of LDHA, GLUT1 and HK2 suggest an increase of metabolic activity in both vaccinated groups. Taken together, our results support that SARS-CoV-2 vaccination could induces a regulatory profile in human monocytes, but more investigations are needed to understand the training phenotype.

(TS14) Pharmacological approaches to the management of Covid-19 in the Pernambuco state: a pharmacist's note in municipal pharmaceutical assistance

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Background: Facing the challenges imposed by the Coronavirus disease 2019 (COVID-19) pandemic, the strain of health systems in establishing planned and integrated actions based on scientific evidence for the clinical and pharmacological management of the infection became evident. Objectives: To evaluate the pharmacological approaches adopted by the municipalities of Pernambuco State for the management of COVID-19. Methods: A cross-sectional study was carried out with pharmacists who worked between March 2020 and March 2021 in the municipal Pharmaceutical Assistance (PA). They were recruited electronically through email from lists provided by the State PA Management and submitted to a semi-structured questionnaire on the Google docs platform. The survey was divided into sections: pharmacist profile; characterisation of the municipality concerning PA; pharmacological management of COVID-19; municipal PA during the pandemic; and pharmacist perceptions during the pandemic. This study was approved by the Federal University of Pernambuco Ethics in Research Committee followed by registration No. 4.682.797. Results: Among 185 municipalities in Pernambuco, pharmacists from 35 (18.91%) participated in the study. The most dispensed drugs for COVID-19 management were azithromycin (88.8%); dipyrone (80.5%); prednisone (63%) and ivermectin (55.5%). Regarding therapeutic purposes, 41.7% of the pharmacists stated that the drugs were dispensed for prophylactic and curative purposes. 66.6% of pharmacists noted that the pharmacological treatment protocol for COVID-19 management was available in the corresponding municipalities. Worthy noting that in 44.4% of these protocols the pharmacists were out of the elaboration team. When asked about the organization of the PA, the presence of the Pharmacy and Therapeutics Commission (PTC) was reported by only 22.2% of the participants. Conclusions: The availability to population of medications without established efficacy and safety for COVID-19, and the absence of PTC and pharmacists in several municipalities point to significant inconsistencies in municipal PA. Such weaknesses can be strategic axes for developing pharmaceutical service improvement policies.

Posters Abstracts

THEMATIC AREA:

Biotechnology and Natural Products

Metabolomics approaches to determine stilbenoids and phenantrenel derivatives from Orchidaceae with potential trypanocidal and cytotoxic

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Orchidaceae is a family with great pharmacological interest due to the presence of phenanthrenic and stilbenoid derivatives, which are compound with biological properties such as cytotoxic against tumoral cells. Although Orchidaceae species have been the aim of several studies, the Brazilian species are underexplored yet. This work aimed to obtain enriched extracts stilbenoid and phenanhrenic derivatives from leaves, roots and bulbs of *Cymbidium* sp and *Cattleya nobilior* using different solvents, to evaluate the anti-*Trypanosoma cruzi* and cytotoxic activities and to perform metabolomic and statistical analyses to determine the bioactive compounds. The chemical analysis were performed by liquid chromatography coupled to diode array detector and mass spectrometer (LC-DAD-MS). Ninety-three constituents were annotated, and of these, 20 were isolated including *O-glycosylated* flavonoids and several stilbenoid and phenanthrenic derivatives. The dichloromethane:methanol extracts at ratios 95:5 (DCM:Me95) were the most active against *T. cruzi* showed IC50 of 42.5 µg/mL (DCM:Me95–root-*Cymbidium*.sp) and 82.9 µg/mL (DCM:Me95–root–*C.nobilior*), while against tumor cells (MCF-7) were the samples DCM:Me95–root–*C.nobilior* revealing an IC50 of 10.1 µg/mL. From the metabolomics and statistical analyses, forty-eight compounds showed a positive correlation with anti-*T. cruzi*, and the greatest correlation were with the metabolites derived from fenanthro[4,3-b]furan, phenanthrenic derivative, dihydrophenanthrenic derivative, and the stilbenoid derivatives such as muscatylline, gigantol and batatasin III. These the last two compounds were isolated and identified by NMR and gigantol is an important antitumoral and antiangiogenic compound. This study demonstrates the highlighted potential of Brazilian species of Orchidaceae to find metabolites active for antitumoral and anti-*T.cruzi* evaluations focused in phenantrenes and stilbenoids.

In silico characterization of L-asparaginase of a new Penicillium species isolated from Cerrado

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L-asparaginase is an important enzyme in the treatment for Acute Lymphoblastic Leukemia (ALL) due to its ability to hydrolyze L-asparagine. The clinical preparations of this enzyme are derived from a bacterial source and its use is often associated with serious adverse reactions. Therefore, the search for new sources of L-asparaginase is relevant. The objective of this work was to the in-silico characterization of the L-asparaginase of a new Penicillium species. The new fungus was isolated from the soil of the Cerrado and identified by the precise morpho-molecular – Penicillium cerradense. The genetic sequence coding for the L-asparaginase was obtained after carrying out a full genome sequencing. The enzyme sequence of L-asparaginase from P. cerradense was subjected to structural modeling and in silico characterization. In SWISSMODEL-Expasy, the enzyme presented as tetramer-forming and 46% identity to L-asparaginase from Erwinia chrysanthemi (cod: PDB 5i4b.1.A). In ab initio, by I-TASSER presented the possible conformation of the active site and the design of a structural model of the enzyme. In functional predictions (Gene Ontology) the sequence under analysis was presented with molecular function of asparaginase activity, metabolic process of asparagine, cellular component of the periplasmic space, and low score for dual asparaginase/glutaminase activity. In silico characterization (BLAST/NCBI ProtParam/Expasy, SignaIP 5.0) the identified protein fragment showed 378 amino acids, molecular weight of 39 kDa, the presence of a signal peptide with 17 amino acids, pI 5.13, aliphatic index 97.25, positive hydropathy (0.256). This work presented prediction of characteristics and possible performances of the L-asparaginase from P. cerradense which can support the improvement of this enzyme production.

Chemical characterization by UPLC/Q-ToF-MS/MS of Coffea arabica L. leaves extract

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Background: Coffee belongs to the Rubiaceae family and the Coffea genus, which includes several species. The species *Coffea arabica* L., known as arabica coffee, and *Coffea canephora*, popularly known as conilon or robusta coffee, stand out, since they are the most used for the preparation of the coffee beverage. Coffee leaves represent an important by-product of coffee beans processing and are widely available as sources of bioactive compounds. Objectives: This study aimed to evaluate the chemical composition of the lyophilized ethanol extract of arabica coffee leaves (EE-CAL). Methods: The chemical characterization of EE-CAL was performed using ultra-performance liquid chromatography coupled to a quadrupole time-of-flight mass spectrometry (UPLC/Q-ToF-MS/MS). Retention time, mass spectra and fragmentation patterns were compared with literature and standards for identification of compounds. Results: The chemical analysis of EE-CAL revealed the presence of compounds from alkaloid class, such as trigonelline and caffeine, in addition to the phenolic compounds such as quinic acid, 5-caffeoylquinic acid (5-CQA), caffeic acid-O-hexoside, mangiferin, (epi)catechin, (epi)catechin monoglucoside and procyanidin trimer. Conclusions: Most of the compounds found in EE-CAL such as trigonelline, caffeine, quinic acid, 5-CQA, caffeic acid-O-hexoside, mangiferin, (epi)catechin, (epi)catechin monoglucoside and procyanidin trimer were described in the literature as presenting several biological activities. The results of this research suggest that coffee leaves, a by-product, is an interesting source of bioactive compounds. Furthermore, this is the first time that caffeic acid-O-hexoside, (epi)catechin monoglucoside and procyanidin trimer have been detected in coffee leaves. Acknowledgements: This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001, and by Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG – APQ-02555-18).

Advanced therapy medicinal products in Brazil: conceptual and regulatory panorama

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Introduction: Advanced therapy medicinal products (ATMP), considered special medicines, require Anvisa approval for use and marketing authorization in Brazil. They include advanced cell therapy, tissue engineering and gene therapy products, which, due to their complexity, innovation and risks, optimized regulatory channels for their development and life cycle monitoring. Understanding the risks related to the new therapeutic product helps to determine the safe conditions for its development and future approval for clinical use, through the establishment of risk mitigation measures. The objective of this study is to briefly present the Brazilian regulatory model applied to ATMP, considering their development cycle, approval and post-marketing monitoring with a focus on risk and safety analysis in line with models applied in other countries. Methods: The narrative review was used by analyzing documents from the databases of the websites of regulatory agencies: Food and Drug Administration(FDA),European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency (PMDA) Japan and National Health Surveillance Agency (Anvisa), as well as documents from the International Council for Harmonization of Technical Requirements for Pharmaceutical Products for Human Use (ICH), Pharmaceutical Inspection Cooperation Scheme (PIC/S) and the World Health Organization (WHO). Results: The regulatory model applied to biological medicines is used in Brazil and in the world, with due particularities and specific requirements for pre-clinical and clinical trials, in the search for positive evidence of the benefit-risk profile and in the definition of critical attributes of quality to demonstrating that the product is safe, efficacy and of high quality available to the population. The approval models for these products in Brazil adapt to the characteristics of the technology and the target population of patients, with accelerated and prioritized regulatory analysis, the use of approval conditioned by risk controls and specific long-term monitoring, especially related to rare diseases and without other therapeutic alternatives. Conclusions: Timely access to the ATMP with safety, efficacy and quality involves innovative regulatory elements that include long-term monitoring of safety and efficacy and adaptive pharmacovigilance requirements, as well as adaptations in Good Manufacturing Practices and mechanisms of traceability of materials, products and patients.

Therapeutic Potentials of Hesperetin-Hydroxypropyl- γ -Cyclodextrin on Adipose Tissue in a Rat Model of Polycystic Ovary Syndrome

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Background: Polycystic ovary syndrome (PCOS) is a multi-factorial endocrine disorder associated with hyperandrogenism, ovarian dysfunction, and obesity. Women with PCOS appear to be more likely to manifest an abnormal accumulation of fat in the abdominal region. The excess adiposity, especially in the presence of androgen hypersecretion, exacerbates the hormonal, metabolic, and clinical features of PCOS. We aim to investigate the potential therapeutic effects of hesperetin-hydroxypropyl-γ-cyclodextrin complex (HST-OH-γ-CD), in adipose tissue, on the letrozole-induced rat model of PCOS. Methods: Wistar albino rats were randomly dividided into four groups: normal control, PCOS control, metformin (20 mg/kg/day) and HST-OH-γ-CD (200 mg/kg/day) treated. PCOS was induced by letrozole (1 mg/kg) dissolved in (CMC 0.5%) for 21 days. The treatments were carried out orally for another 21 days. At the end of the experiment, the body and retroperitoneal adipose tissue (RAT), periovarian adiposus tissue (PAT) weight of rats were measured. Body fat was calculated as the sum of the weight of individual fat deposits as follows: GC = retroperitoneal fat + visceral fat (periovarian fat). Data were statistically analyzed by GraphPad Prism 7 programme. Results: The administration of letrozole for 21 days resulted in a gain in body weight of the animals, as well as in a greater accumulation of fat in the periovarian and retroperitoneal fat pads. The treatment with HST-OH-γ-CD did not modify body weight gain, but RAT (1.01 ± 0.38 versus 1.48 ± 0.38 g) and PAT weights (2.9 ± 0.5 versus 4.08 ± 1.2 g) were found to be decreased significantly ($p < 0.05$) as compared with the PCOS control group. Furthermore, compared to the PCOS group, the adiposity index was lower (p<0.05) in the groups treated with HST-OH-γ-CD. Conclusions: The results suggest that treatment with HST-OH-γ-CD reverses PCOS-induced alteration in adipose tissue, possibly by regulating intracellular lipid accumulation. Therefore, HST-OH-γ-CD intervention is a potential therapeutic approach for PCOS. Acknowledgements: This study was financed in part by the Conselho Conselho Nacional de Desenvolvimento Cientifico e Tecnologico – Brasil (CNPq), and the Coordenacao de Aperfeicoamento de Pessoal de Nivel Superior - Brasil (CAPES).

Heterologous expression of Penicillium sizovae L-asparaginase in Escherichia coli BL21(DE3)

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Background: L-ASNase is the first therapeutic enzyme with antineoplastic properties. Its main use is in the treatment of acute lymphoblastic leukemia (ALL). ALL is a malignant neoplasm of B or T lymphoid progenitor cells with rapid progression and corresponds to 75% of leukemia diagnoses in children and teenagers. Bacteria (*Escherichia coli* and *Dickeya chrysanthemi*) are the current source available of L-ASNase, besides their therapeutic efficacy, they share several hyper sensibility mechanisms related to its toxicity. In order to reduce undesirable effects, other L-ASNase sources have been investigated. Fungal source stood out, however, presents low yield. Objectives: Heterologous expression of *Penicillium sizovae* L-ASNase in *E. coli* BL21(DE3) system. Methods: L-ASNase *P. sizovae* sequence optimized was used in the construction of the pET28a expression vector, containing a His-tag tale in the N-terminal sequence (pET28aPs). Ten recombinant clones were screened by PCR to confirm the transformation. Positive clones were then cultivated in LB medium. Induction experiments started with 0.5 mM of IPTG after 4 h of pre-growth (OD600 1.4). After 18 h of induction, cells were collected and submitted to lysis in Tris-HCl pH 8.6, through sonication. At least, the crude extract was subjected to electrophoresis in SDS-PAGE and Western-Blotting to confirm the expression of L-ASNase. The activity was measured by the quantification of β-hydroxamate aspartic. Results: Through the PCR analysis, it was possible to confirm that all the ten *E. coli* clones were successfully transformed with the pET28a vector with the *P. sizovae* L-ASNase gene (pET28aPs1 to 10). After SDS-PAGE analysis, a protein band with the estimated molecular mass of recombinant L-ASNase was visualized only in the insoluble fractions. However, western-blotting results demonstrated the presence of L-ASNase only in the insoluble fraction of pET28aPs2, 4, 8, 9, and 10. No enzyme activity was found, which might indicate that the enzyme was overexpressed in an inactive conformation, in the form of inclusion bodies. Further experiments of solubilization and refolding are required to obtain L-ASNase in its native and active conformation. Conclusion: This work demonstrated the expression of *P. sizovae* L-ASNase in an *E. coli* system successfully, however, the enzyme was expressed in the inclusion bodies form. More studies are necessary to obtain an active L-ASNase.

Chemical composition and biological activities of two Myrcia species

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The Atlantic Forest is one of the most biodiverse Brazilian biomesand has important domains, one of them the restingas. The Myrtaceae family is one of the most expressive families in terms of the number of species in Restinga, and several of them, such as Myrcia neuwiedeana (O.Berg) E. Lucas & C.E. Wilson. and Myrcia neobrasiliensis A.R. Lourenço & E. Lucas have never been studied from a chemical point of view. Therefore, this work aimed to determine the chemical profile of these two species and evaluate the antioxidant capacity and inhibition of enzymes involved in the metabolism of carbohydrates. The chemical profile was determined by chromatographic and spectrometric analyses, such as GC/MS and ESI(-)FT-ICR MS. The antioxidant activity was evaluated by ABTS and DPPH inhibition; the enzyme inhibition was determined in vitro against α-amylase and α-glucosidase. The aerial parts'methanolic extracts and their respective hexane, dichloromethane, ethyl acetate, and aqueous fractions were analyzed by GC/MS. Sesquiterpenic and triterpenic compounds were identified in the hexane fractions. Through ESI(-)FT-ICR MS, methyl gallate, quinic acid, quercetin, myricetin, quercitrin, myricitrin, and triterpenic acids were identified in both species (crude extracts' ethyl acetate fractions). More over, α- and β-amyrin were isolated from M. neuwiedeana. Both species showed antioxidant activity, and the ethyl acetate fraction of M. neobrasiliensis was the most active in the ABTS radical assay (IC50= 0.42µg/mL), statistically similar to gallic acid, and used as reference (IC50= 0.31µg/mL). Regarding α-glucosidase inhibition, M. neuwiedeana crude extract presented IC50=10.22µg/mL, while acarbose (reference compound) presented IC50=19.14 µg/mL. The M. neuwiedeana aqueous fraction was the most active on α -amylase (IC50=5.74µg/mL) while acarbose presented IC50=1.41µg/mL. The present work reported for the first time, concerning M. neuwiedeana and M. neobrasiliensis, information about the chemical composition and biological activities. These results contribute to the knowledge about Brazilian flora and reaffirm the great importance of the Myrtaceae species.

Determination of matrix effect of herbal drugs

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Background: With popularity of herbal drugs (HD), concerns about the quality and safety of these products have increased. Mycotoxins produced by fungi that infect plants and are potentially hazardous to human health. In Brazil, reports about the presence of mycotoxins in HD are scarce. Objectives: The objective of this work is to determinate the matrix effect (ME) of HD for aflatoxins (AFB1, AFB2, AFG1 and AFG2), citreoviridin (CTV), deoxynivalenol (DON, 3AcDON and 15AcDON), fumonisins (FB1, FB2, FB3), ochratoxin A (OTA), and zearalenone (ZEN) using liquid chromatography tandem mass spectrometry (LC-MS/MS 4000 QTrap, Sciex). Methods: Three different extraction protocols based on the work by Andrade et al. (2017) were tested: ultrasonic bath (UB) for 5 and 15 minutes or shaking at 200 rpm for 15 min. The QuEChERS method was also tested using different partition salts and adsorbents (Cho et al., 2018; Mozzaquatro et al., 2020). The matrix effects were tested using 10 different HD. Results: In the evaluation of ME in P. edulis, no significant differences were observed for all the analytes when comparing UB or shaking It was observed less ME for FBs (- 33 to -82%) and OTA (-75 to – 81%) and for the others analytes the suppression was more than -80%. The evaluation of the partition salts (MgSO4 and CaCl2, citrates) and adsorbents (PSA and C18) in the QuEChERS method was done using G. biloba. The ME was lower, ranging from -14% (FB2) to -79% (CTV). When compare this different QuEChERS no significant difference for AFs, DON and CTV were observed. For ZEN and FBs the use of citrate and C18 showed higher ME. However, the opposite result was observed for OTA. In general, less ME was found for P. edulis compared to G. biloba. Conclusions: Addition of a purification step (QuEChERS) was important for ME for all analytes and used of different adsorbent and partition salt can influence the ME. However, this is dependent of the matrix used, and is probably correlated with the amount of coeluents present in the matrix. So, the used of a mix with different HD is more precise as representative blank matrix. Acknowledgments: Fundo de Defesa de Direitos Difusos (MJ) and FAP-DF.

The single-chain type antibody NUsc1 binds to neurotoxic Aβ peptide oligomers with high affinity as determined by Surface Plasmon Resonance

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Background: Alzheimer's Disease (AD) is characterized by the accumulation of β-amyloid peptide aggregates, with soluble oligomers being the main species responsible for synaptic loss and consequent dementia. In previous studies, artificial single-chain antibodies against Aβ oligomers (AβOs) were selected by our group, including NUsc1. Since then, we have shown that NUsc1 reduces oxidative stress induced by AβOs in neuronal cultures, in addition to reverse memory impairment in AD mouse models. Here, we followed the interaction between NUsc1 and AβOs using surface plasmon resonance (SPR). Objectives: Evaluate the specificity and affinity of binding of scFv antibody NUsc1 to Aβ oligomers. Methods: A CM-5 chip was functionalized with myc-tagged NUsc1 indirectly, through binding to the anti myc-tag IgG antibody 9e10. The interaction with synthetic AβOs was analyzed by SPR. Alternatively, AβOs were incubated with magnetic beads functionalized with either NUsc1 or a control scFv, and the interaction with oligomers was assessed by ELISA. In parallel, the phage-bound NUsc1 antibody was tested against AβOs or LysOs by ELISA. Results: Immobilization of NUsc1 to the chip via 9E10 and the binding of AβOs to immobilized NUsc1 were readily observed. AβO-concentration dependence assay revealed affinity of NUsc1 to AβOs is in the low nanoM range. The strong signal seen when NUsc1 is used to detect AβOs contrasted with a low signal observed with lysozyme oligomers (LysOs), another neurotoxic protein, demonstrating specificity of NUsc1 to Abeta oligomers. In line with this, we have also found that AβOs detection by NUsc1 was significantly higher than when a control scFv was used. Conclusions: We were able to monitor the formation of the NUsc1/AβO complex and to determine the affinity of NUsc1 for AβOs by SPR. We also obtained robust data indicating a high selectivity of NUsc1 for AβOs. These results reinforce the potential of NUsc1 as a diagnostic and therapeutic agent against Alzheimer's-associated neurotoxic AβOs.

Heterologous expression of L-asparaginase from Fusarium proliferatum in native and mutated Escherichia coli BL21 (DE3)

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Background: L-asparaginase (L-ASNase) is an enzyme with hydrolytic properties of the non-essential amino acid L-asparagine that have an important role in the development of malignant cells such as those from Acute Lymphoblastic Leukemia (ALL). The scenario of adverse reactions from the asparaginase produced by a prokaryotic organism is one of the approaches that arouses interest in the search for new sources of this enzyme and mainly to produce L-asparaginase of fungal origin. Objectives: The aim of this work was to express L-ASNase of *Fusarium proliferatum* in *E. coli* expression system. Methods: Native and mutated *E. coli* BL21 (DE3) cells were transformed using the pET-28a expression vector, containing *F. proliferatum* asparaginase. Isopropyl β-D-1-thiogalactopyranoside (IPTG; 0.45 mM) was added to induce enzyme expression. The samples were analyzed in SDS-PAGE 12% and the detection of L-ASNase expression was performed by Western blot. Results: The transformation of 10 clones of both *E. coli* BL21 (DE3) colonies with pET-28a L-ASNase_*Fp* vector has been confirmed by PCR. The recombinant L-asparaginase produced by 3 clones was confirmed by Western Blot analysis using antibodies against the His-tag of the protein produced. After cultivation and extraction, the gels containing insoluble samples showed bands with greater intensity at the height of approximately 40 kDa. Conclusion: Considering that *in silico* analyzes predict that the molecular weight of L-asparaginase is 40 kDa, it can be inferred that the bands represented in the SDS-PAGE and Western Blot correspond to that of the recombinant enzyme. However, as the enzyme is predominantly present in the insoluble fraction, it is not possible to presume its activity, probably because it is concentrated in inclusion bodies form. Further experiments should be carried out with the aim to evaluate enzymatic activity. Moreover, the discovery of novel L-asparaginase from eukaryote may lead to safer alternatives for ALL treatment due to their potential to be less immunogenic.

Evaluation of the antifungal activity of film-forming systems containing pomegranate peel extract (Punica granatum L.)

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Candida species can cause clinically evident infections. Changes in immunity, stress, dysbiosis and use of antimicrobials can result in mucocutaneous candidiasis. The use of natural products, such as *Punica granatum* L. (pomegranate), has been shown to be an alternative in the elimination of fungal infections. In the context of possible pharmaceutical formulations for topical administration, bioadhesive films reduce the frequency of drug administration, which contributes to patient acceptability, treatment adherence and pharmacotherapy success. Thus, the objective of this work is to evaluate the antifungal activity of in situ film-forming systems (SFF) containing pomegranate peel extract (ECR). Four formulations were prepared with different types and amounts of polymers , A (18% PVA), B (20% PVA), C (18% PVA + 0.5% sodium polyacrylate) and D (20% PVA + 0.75% sodium polyacrylate) for ECR incorporation in three different concentrations (1.25%, 2.5% and 3.75%). Antifungal activity was evaluated by the well diffusion method against *Candida albicans* (ATCC 24433), *Candida parapsilosis* (ATCC 22019) and *Candida glabrata* strains. (ATCC 2001). Absence of zones of inhibition were observed for the formulations of the blends without extract, with and without preservative, confirming the absence of interference of the polymers in the antifungal activity. The formation of zones of inhibition was observed for all the formulations studied and the increase in the size of the halos was proportional to the increase in the concentration of ECR in the formulations. Formulations A and D, there were significant differences between concentrations and 3.75% was the most effective concentration for C. *albicans*, C. *parapsilosis* and C. *glabrata*. In formulation B, no statistical difference was found between the concentrations analyzed. In formulation C, there was no difference between concentrations for C. *albicans*, however for the others, the most effective concentration was 3.75%. From the results obtained, it can be suggested that the proposed film-forming solution formulations are promising for use in the treatment of mucocutaneous candidiasis, and the 3.75% w/w concentration is considered appropriate for the intended purpose.

Antioxidant activity by aqueous extract and the gel formulation of Psidium guajava L.

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Background: Exposure to ultraviolet radiation is an important risk factor for the development of skin diseases. Photoaging by chronic exposure to UV radiation is related to excessive oxidative stress and decreased antioxidant capacity. One approach to prevent or treat these ROS-mediated disorders is based on the administration of antioxidant compounds, including bioactive plant compounds, as an effort to restore skin homeostasis. Thus, derivatives of Psidium guajava L. (Myrtaceae), a species widely used in folk medicine around the world, were evaluated in this study. Objectives: This work aims to evaluate the antioxidant activity of aqueous extract (EAPG) and the gel formulation of P. guajava L. Methods: The P. guajava L. leaves were collected in Brasília, Federal District, Brazil. The plant material was dried and powdered in a knife mill. The aqueous extract was obtained by infusion and lyophilized. A gel formulation containing 0.5% EAPG was prepared. The antioxidant activity of EAPG and formulation were evaluated using the DPPH• reducing activity methods and the ferric reducing antioxidant power (FRAP) assay. Ascorbic acid was used as positive control in both assays. All analyses were performed in triplicate, and data are expressed as the mean ± standard deviation. The statistical analyses were accomplished using the computer software GraphPad Prism Version 6.0. Results: The IC50 of the antioxidant activity evaluated was 6.35 ± 1.02 µg/mL for the EAPG and 9.22 ± 1.93 µg/mL for the formulation in the DPPH• assay. In the FRAP assay, values of 14.42 ± 0.58 µg/mL of EAPG and 24.42 ± 1.34 µg/mL of formulation were equivalent to 60 µM of Fe2+. Ascorbic acid antioxidant capacity by DPPH• and FRAP assays revealed IC50 values of 3.25 ± 0.19 µg/mL and 5.00 ± 0.22 µg/mL were equivalente to 60 µM of Fe2+, respectively. Conclusions: The results obtained in the antioxidant assays show good antioxidant power of the samples tested. Greater antioxidant power was obtained by the extract, in comparison to the formulation. Both activities were lower than the positive control.

Analytical standardization and antioxidant properties of the ethyl acetate extract of the leaves of Celtis iguanaea (Jacq.) Sargent (Cannabaceae)

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Background: Over the last decade our research team have been investigating the several pharmacological properties of the leaf extracts of Celtis iguanaea, known as “esporão-de-galo” in the Brazilian folk medicine. Recently, we have shed light to the remarkable anti-inflammatory and antinociceptive effects of the ethyl acetate extract of the leaves of C. iguanaea (EAcCI) in pre-clinical trials in rodents. Objectives: To standardize the EAcCI and to evaluate its in vitro antioxidant properties. Methods: The EAcCI was obtained by Soxhlet extraction (10% m/v, 72 h) and rotaevaporated (< 40°C) under vacuum up to attain 150 mg/mL. A reversed phase (C18) HPLC-PDA exploratory gradient with acetonitrile and H2O plus 0.1% formic acid (60 min, 200 – 800 nm) was performed. The classes of phytochemicals containing in the extract were tentatively identified by comparing the UV spectra with the data published elsewhere. Peak purity above 95% were considered. The total polyphenolic content (TP, % m/m; gallic acid equivalent) and total flavonoid content (TF, % m/m; rutin equivalent) were determined by spectrophotometry (Folin Ciocalteu and AlCl3 methods, respectively). The overall antioxidant capacity of the EAcCI was determined by differential pulse (DPV) and squared wave (SWV) voltammetry, that rendered the electrochemical index (EI). Ascorbic acid was used for comparison purposes. Results: The HPLC-PDA analysis confirmed the presence of at least 12 phytochemicals in the sample, i.e., 2 phenolic acids (1 cinnamic and 1 benzoic acid derivatives) and 10 flavonoids (5 flavones and 5 flavanones). The TP and TF in the EAcCI were of 0.35 ± 0.03 % and 0.49 ± 0,01 %, respectively. Concerning the antioxidant activity, 5 anodic peaks were evidenced for the EAcCI in the DPV analysis (Ep1a = 0.015 V, Ep2a = 0.254 V, Ep3a = 0.37 V, Ep4a = 0.844 V and Ep5a = 1.06 V); and the SWV revealed 2 anodic peaks and 1 cathodic peak (Ep1a and Ep1c = 0.254 V). Moreover, the EI was 42.64 µA/V, which is 2.6-fold greater than the obtained for ascorbic acid (16.33 µA/V). Conclusions: The flavonoids are the main phytochemicals containing in the EAcCI and its overall antioxidant capacity is noteworthy, thus justifying further investigations of its efficacy in experimental models involving the oxidative stress (e.g., cancer and Alzheimer).

Comparing the pharmacognostic features of herbal drugs of Celtis iguanea leaves from São Sebastião do Oeste – MG and Campinas – SP

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Background: In Brazilian folk medicine the Celtis iguanaea (Jacq.) Sargent (Cannabaceae) is used to remedy several inflammatory ailments. These ethnopharmacological claims have attracted the attention of researchers and substantial amount of evidence regarding the efficacy and safety of herbal derivatives of this species have been reported. Owing to this pharmacological potential and the prospects for developing standardized phytomedicine, evaluating the physicochemical quality of herbal raw materials of C. iguanaea is fully justified. Objectives: To compare the pharmacognostic features of herbal drugs obtained from C. iguanaea specimens of different origin. Methods: Leaf samples were collected in the beginning of 2022 Brazilian fall (March 27th to April 21th) from several specimens located at L1 (20°16'30.9 "S - 44°56'40.8 "W; São Sebastião do Oeste – MG), L2 (20°19'21.2 "S - 45°03'24.1 "W; São Sebastião do Oeste – MG) and L3 (22°51'53.09 "S - 47°03'22.3 "W; Campinas – SP). The samples were oven-dried bellow 40°C, ground in a knife mill a stored sheltered from light and moisture at room temperature. We have accessed the moisture content (Mc), total (Tac) and acid insoluble ash (AIac) contents and mean particle diameter (D50) according to the Brazilian Pharmacopoeia 6th Ed.; and the total phenolic (TPc) and flavonoid (TFc) contents were determined by using widely quoted spectrophotometric methods. Experiments were all performed at least in triplicate. The data were compared by ANOVA followed by Tukey's post-hoc test. Results: For samples L1, L2 and L3, respectively: Mc was 12.33 ± 0.45%, 11.80 ± 0.32% and 11.45 ± 0. 18%; Tac was 12.9± 0.1%, 17.8 ± 0.6% and 23.3 ± 0.8%; AIac was 9.1 ± 1.3%, 11.2 ± 1.3% and 14.3 ± 1.8%; D50 was 425 µm, 586 µm and 501 µm; TPc was 0.31 ± 0.10%, 0.33 ± 0.08% and 0.14 ± 0.05%; and TFc was 0.33 ± 0.09%, 0.36 ± 0.14% and 0.22 ± 0.06%. Conclusions: There were not statistically significant differences within samples L1 and L2, but these were significantly different of L3. Therefore, locality influences on the pharmacognostic characteristics of C. iguanaea, especially in total and acid insoluble ash contents. Further studies of seasonality and chemical variability will be the target of our research team.

Effect of cranberry extracts on antioxidant enzymes and lipid peroxidation in cell culture

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Cranberry (Vaccinium macrocarpon Antion.) is recognized for its antioxidant activity. Its chemical profile includes anthocyanins, pro-anthocyanidins, phenolic acids,flavonoids and triterpenes. In this work, the effect of the total cranberry extract (ETCb), and its aqueous (FrA-Cb) and ethyl acetate (FrAcOEt-Cb) fractions were evaluated on the activity of enzymes catalase (CAT), superoxide dismutase (SOD), and the lipid peroxidation in HFF-1 (human foreskin fibroblasts) culture after induction of oxidative stress by UVA radiation. The preliminary results for SOD showed that, at concentrations of 25, 50 and 100 µg.mL-1 cranberry extracts decreased the activity of this enzyme. On the other hand, it was observed an increase in CAT activity on cells treated with the extracts. Fibroblasts treated with ETCb showed a CAT activity of 440.6 ± 1.83; 380.66 ± 4.22 and 119.54 ± 18.72 ΔH2O2 µM/min/mg of protein at sameconcentrations, the FrA-Cb promoted a similar effect, resulting in CAT activities of 279.26 ± 0.49; 244.5 ± 1.349 and 227.25 ± 0.129 ΔH2O2 µM/min/mg of protein for the respective 25, 50 and 100 µg.mL-1 concentrations tested. Finally, FrAcOEt-Cb, at concentrations, 25 and 100 µg.mL-1, increase CAT activity activity, resulting in 124,43 ± 8.01 and 93.48 ± 2.17 ΔH2O2 µM/min/mg protein. The treatment with FrAcOEt-Cb at 50 µg/mL-1 resulted in a decrease of CAT activity in the cells when compared to control. In the lipid peroxidation assay it was observed a decreasing amount of the MDA species in fibroblasts treated with the same concentrations of extracts. ETCb caused a MDA decrease of 2.72; 2.97 and 3.14 times, treatment with FrAcOEt-Cb showed a notorious effect, showing a MDA decrease of 3.50; 3.83 and 5.02 times, and for FrA-Cb a decrease in MDA concentration was 2.08; 2.71 and 3.25 times, when compared with the control. The results obtained so far allowed suggest that the total cranberry extract and its fractions showed a positive effect in CAT activity, as well as attenuated the lipid peroxidation caused by the oxidative stress produced by UVA radiation.

Keywords: cranberry, SOD, catalase, lipid peroxidation

Curcuma longa and its use for autism symptoms: review

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Background: Autism spectrum disorder (ASD) is defined as a complex and heterogeneous group of neuropsychiatric disorders that affect brain development. The plant *Curcuma longa* is popularly known as turmeric. One of the compounds found in this plant (curcumin) has shown neuroprotective properties of this substance in neurons, in both *in vitro* and *in vivo* models. Objectives: This study aimed to verify the existence of benefits related to the use of *Curcuma longa* in the treatment of autism. Methods: Experimental articles and reviews, written in English and Spanish, were searched on May 22th, 2022, with a time restriction (2015 to 2022). The search was performed in six different databases. Those who focused on the *in vitro* and *in vivo* evaluation of the effects of *Curcuma longa* and its bioactive components in the treatment of autism disorder were eligible. Results: Data we found only evaluated and cited the main bioactive present in *Curcuma longa* (curcumin). In phase 1 of study selection, 3,484 citations were identified. After removing the duplicates, only 778 citations remained. After a comprehensive evaluation of titles and abstracts, 744 studies were excluded, and 34 articles were eligible at the end of phase 1. Among the 34 articles, after a complete reading of the articles, only three were associated with the plant as an object for treatment or prevention of ASD. These studies have found: improvement in neurodevelopmental delays; alleviation of neurobehavioral, biochemical and molecular alterations; neuroprotective effects on cells exposed to BPA (bisphenol A); and significant improvement in memory and learning. Conclusions: Given that the included articles demonstrated benefits in using curcumin (one of the main bioactives of *Curcuma longa*) in ASD models of rats. It is possible to suggest that curcumin can be effective for improving symptoms related to ASD, and also prevent the development of thist neurodevelopmental disorder. However, further studies, especially clinical trials, must be carried out.

Characterization of polysaccharide obtained from Sterculia foetida gum

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Polysaccharides have several properties of industrial interest and are used in the most diverse areas, such as food, cosmetics, and pharmaceuticals. Trees of the genus Sterculia are known to produce acidic polysaccharides with high viscosity. The horse chestnut (Sterculia foetida L.) is an exotic Asian tropical tree, found in India, Vietnam, and Sri Lanka. Due to its physicochemical characteristics, it has promising characteristics as a hydrophilic matrix in controlled drug delivery systems and as a pharmaceutical excipient. However, that species is little explored and there is a lack of information regarding the characterization of the material. The present work aimed to improve the method of isolation of Sterculia foetida gum and characterize the biopolymer extracted from it, to obtain new information about this new material. For the isolation and purification of the material: (1) starting with the separation of the exudate and husks, followed by dissolution, agitation, filtration, precipitation, and drying; (2) dissolution, stirring, and heating for a short period (2h), filtration, precipitation, and drying; (3) dissolution, stirring, heating for a long period (24h), filtration, precipitation, and drying. Protocol 3 showed the highest yield (40.5%) and was selected for characterization. The polysaccharide was characterized by Fourier Transform Infrared Spectroscopy, texture analysis, and size determination by Gel Permeation Chromatography. The phytochemical identification was performed by colorimetric methods for the determination of alkaloids, tannins and phenols, organic acids, and reducing sugars. The isolated gum presented a positive result for organic acids and reducing sugars, and the absence of alkaloids, saponins, tannins, and phenols, which were not observed in the other protocols. Infrared spectroscopy showed that the gum has functional groups characteristic of natural gums (aliphatic groups) and Sterculia gums (carbonyl and acetyl groups). Sterculia foetida gum had an Mw of 1.20 x 107 and polydispersity index of 5.8. In the texture analysis, hardness (11.43 ± 0.13), consistency (136.43 ± 1.40), cohesiveness (-7.18 ± 0.18),viscosity index (-8.13 ± 0.18) were identified. 0.75) in 1% w/v solution. Thus, with the protocol used in the present study, the gum presented a good yield and properties found in Sterculia gums such as functional groups, size, and texture, which can be applied in the isolation of Sterculia foetida L. polysaccharide.

Ultrasound-Assisted Extraction of polyphenols from the fruit peel of Isabel grape (Vitis labrusca) and jaboticaba (Myrciaria cauliflora)

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Background: Owing to their remarkable contents of bioactive phytochemicals such as phenolic acids and flavonoids, the fruit peels of grape (Gp) and jaboticaba (Jp) have been reusing in the development of nutricosmetics and nutraceuticals. Besides adding value to the productive chain of these foods, this strategy can reduce the environmental impacts that may be caused by the inappropriate disposal of such by-products. Objectives: To optimize the recovery of polyphenols from Gp and Jp by Ultrasound-assisted extraction (UAE) allied to Box-Behnken Design (BBD) and Response Surface Methodology (RSM). Methods: The fruits of Isabel grape and jaboticaba (harvest 2021) have been purchased in markets of Divinópolis – MG. After removal of the pulp and seeds, the peels were dried at room temperature, ground and stored under refrigeration. Such herbal drugs were evaluated regarding moisture content (MC, % m/m) and total ash content (AC, % m/m). For optimizing the UAE, we used a BBD with three factors and three levels (33, 15 runs). The process variables that we have investigated and their levels were the ethanol content (EC; 20, 50 and 80% v/v); herbal drug/solvent ratio (D/S; 1, 3 and 5% m/v); and extraction time (T; 30, 45 and 60 min). A frequency of 40 KHz and potency of 220 W were fixed throughout the experiments. The recovery of total phenolics (TP, % m/m; tannic acid equivalent) was selected as in-process performance indicator, being determined by spectrophotometry (n ≥ 3). The RSM was used to determine the factors significantly affecting the process and to predict optimized extraction conditions. Results: The MC and AC for the Gp and Jp were of 8.9 ± 0.2 % and 0.06 ± 0.001%; and 11.5 ± 0.3 % and 0.02 ± 0.001%, respectively. The TP of Gp ranged from 0.45% to 1.26%, for Gp and 3.5% to 14%. According to the RSM, the EC was main factor affecting the TP of Gp, followed by T and D/S (p < 0.05; R2 = 0.94). In turn, the EC was the only factor affecting the TP of Jp (p < 0.05; R2 = 0.87). The first-order interactions between the studied factors did not significantly affect the performance of UAE for both samples. Conclusions: The Jp displayed a more attractive source of polyphenols than the Gp. The optimized TP for Gp was achieved with an EC of 50%, D/S of 1% and T of 60 min; while for Jp it involves the same EC and D/S, but a T of 30 min.

EHMT1/EHMT2 priming exerts anticancer effect on melanoma and lung cancer cell lines

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Background: EHMT family of histone methyltransferases is an attractive target for cancer therapy, as it is dysregulated in several types of cancer. Objectives: Here, we investigated the effects of EHMT1/2 inhibition on MeWo and A549 cancer cell lines. For this, the selective inhibitor of EHMT1/2 -UNC0646- was used and the following processes were investigated: cell proliferation, viability, death, mitochondrial function, migration, and gene expression. In addition, we performed an in silico analysis of the prognostic impact of these enzymes, exploring available data from lung cancer and melanoma patients at OncoLnc. Methodology: MeWo and A549 cells were treated with UNC0646 and by the MTT assay we investigated the impact of EHMT1/EHMT2 inhibition on cell proliferation/viability. Considering IC50 and IC75 determined, we investigated cell apoptosis by Flow Cytometry (Annexin V/PI) and also evaluated LDH production and caspase 3/7 activity by spectrophotometry. In addition, we evaluated the mitochondrial membrane potential using the Rhodamine 123 probe and the migratory capacity of cell lines after EHMT1/2 inhibition. Finally, the transcriptional profile of genes related to proliferation, cell death, and migration was investigated by RT-PCR. Results: EHMT1/2 inhibition compromised the MeWo and A549 viability in a dose-dependent manner. This inhibition also promoted cellular apoptosis as demonstrated by annexin/PI assay, increased LHD secretion, and affected mitochondrial membrane potential. Furthermore, EHMT1/2 inhibition promotes caspase 3/7 activation, beyond affecting the migratory capacity of A549 cell line. Interestingly, the EHMT1/2 inhibition modulates the transcriptional levels of KI67, CASP1, and GSDMD in A549. In contrast, this inhibition promotes BAX, NLRP3, KI67, and CXCR4 modulation in MeWo cell line. Finally, our in silico analysis revealed that high EHMT1/2 expression is related to lower survival in melanoma patients. Conclusions: Our data clearly show that EHMT1/EHMT2 inhibition promotes cell death of MeWo and A549 cancer cells, indicating that these histone methyltransferases can be further explored as an epigenetic target for the treatment of lung carcinoma and malignant melanoma.

Chemometric analysis of commercial samples of Equisetum species after hydroethanolic extraction and acid hydrolysis

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Background: Botanical identification of plant species sometimes is difficult due to macroscopic and microscopic similarity. The misidentification becomes a problem when a species has clinical application, and no studies of interchangeability with others of its genus are available, as is the case for the genus Equisetum (horsetail), which is widely commercialized in Brazil for diuretic purposes. In this situation, the indiscriminate commercialization of similar species compromises the safety and efficacy of medicinal plants, requiring robust tools for achieving unambiguous identification. Objectives: The aim of this work was to use chemometric tools to differentiate samples of 'teas' of Equisetum species after hydroethanolic extraction and acid hydrolysis using TLC and HPLC analytical methods. Methods: Samples from 17 different sources of Equisetum 'teas' were acquired in the local market (Belo Horizonte, MG). Hydroethanolic and acid hydrolyzed extracts were produced and analyzed by TLC and HPLC, respectively. The retention time and peak area data obtained from HPLC were inputted into Hierarchical Clusters (AAH) and Principal Components (PCA) Analyses performed using the mixOmics package in the R software. Results: The results obtained after the TLC analysis of hydroethanolic extracts suggested the grouping of the 17 samples into three species: E. arvense (3), E. giganteum (9) and E. hyamale (5). However, the differentiation between the species E. arvense and E. giganteum raised doubts and an acid hydrolysis was performed. The results from hydrolyzed samples allowed the annotation of 46 chromatographic peaks. After chemometric analysis, we confirmed the grouping of the 5 samples previously suggested as E. hyemale while the other samples were clustered into just a single group, taking HPLC and TLC data into account, suggesting it to be E. giganteum. Conclusion: The application of chemometric analysis as a complementary tool in the chemical identification of species, in addition to demonstrating the analysis bias of less modern techniques, such as TLC, was fundamental in differentiating commercial 'tea' samples from Equisetum species, without botanical evaluation.

Partial in silico evaluation of L-Asparaginase immunogenicity from Penicillium cerradense

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Background: L-asparaginase (L-ASNase) is an enzyme responsible for the amino acid L-asparagine hydrolysis. Due to its mechanism, L-ASNase is used for the treatment of Acute Lymphoblastic Leukemia (ALL). In medicine, L-ASNase is derived from bacterial sources and its use is often associated with serious hypersensitivity reactions and other adverse reactions. Therefore, the study of immunogenicity from new sources of the enzyme is relevant. Objectives: The aim of this work is to predict the immunogenicity *in silico* of the L-ASNase from *Penicillium cerradense*, a new fungus isolated from the Cerrado soil. Methods: The genetic sequence of the *P. cerradense* L-ASNase (L-ASNasePc) was obtained after a complete genome sequencing. The L-ASNasePc sequence was subjected to the T-cells epitopes prediction using MHC-II Binding Predictions/Immune Epitope Database integrating NN-align, SMN-align, combinatory library, Sturniolo, and NETHCIIpan methods with the consensual method. For the epitope's density determination, the relative frequency calculation for immunogenic predicts within linear percentile ≤10. The epitopes density for each protein was determined for eight different alleles. The amino acid sequences available in the Protein Data Bank (PDB) from *Escherichia coli* (3ECA) and *Dickeya chrysanthemi* (JK0) were used to compare L-ASNasePc with L-ASNases from clinical usage. Results: The degree of immunogenicity of L-ASNasePc did not present significant differences with the L-ASNases from *E. coli* and *D. chrysanthemi* for clinical use. Comparing L-ASNasePc with the other L-ASNases, L-ASNasePc showed higher immunogenicity (0.087) than the available enzyme from *E. coli* (0.071), and lower than the *D. chrysanthemi* L-ASNase (0.111). In addition, the L-ASNase from *D. chrysanthemi* presented a higher degree of immunogenicity ($p < 0.05$). Conclusions: These results demonstrated that the L-ASNasePc has a degree of immunogenicity compatible with two L-ASNases from clinical usage. In conclusion, the immune response of the L-ASNases from *E. coli* and *D.chrysantemi* are possibly similar to the L-ASNasePc immune response, to the T-cells epitopes.

THEMATIC AREA:

Drug discovery and Medicinal Chemistry

A New Lignan from Annona squamosa demonstrate cardioprotective effects in vitro

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Ecuamosan, a new furofuran lignan have been isolated the leaves of Annona squamosa (Annonaceae). Escuamosan inhibit the contraction evoked by phenylephrine in rat aortic ring in a concentration-dependent manner, and also showed inhibitory effect on vasocontraction of depolarized aorta with high concentration potassium. The vasorelaxant effect by escuamosan could be attributed mainly to inhibition of calcium influx from extracellular space through voltage-dependent calcium channels or receptor-operated Ca2+-channels, and also partly mediated through the increased release of NO from endothelial cells. The ability of escuamosan to modify vascular reactivity of rat aortic rings incubated with high glucose (D-glucose 55mM) was then evaluated, this alkaloid reverted the endothelium- dependent impairment effect of high glucose in rat aortic rings, in order to explain it protective effect on vascular endothelium, antioxidant activity of escuamosan were assessed using DPPH and FRAP assays. Escuamosan exhibited potent antioxidant activity compared to ascorbic acid which was used as positive control. In conclusion, this lignan showed promising metabolic, vascular effects, and potent free-radical scavenging ability which suggests it potential beneficial use to tackle complex cardiometabolic diseases due to free radical-mediated diseases and its calcium antagonism mechanism.

Synthesis And Evaluation Of Aryl-Alkylpiperazine Compounds As Dual Ligands At H3r And Cholinesterases

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Background: The noteworthy involvement of histamine receptors on cognition has attracted interest of many researchers. The histamine H3 receptor (H3R) is an auto and hetero-receptor that may control the release of several neurotransmitters besides histamine; thus H3R antagonists may increase the release of acetylcholine (ACh), also involved in the cognition. Therefore, the mutual action on pharmacological targets capable of increasing the activity of both histamine and ACh may represent an important alternative in the treatment of dementias. Objective: To synthesize and evaluate a set of aryl-alkylpiperazine derivatives as H3R/cholinesterases ligands. Methods: The structural motifs required for binding at H3R were overlapped to anticholinesterase agents and used as model to design the compounds. These were tested for the ability to inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) at 1 and 100 µM and the most promising were evaluated in full concentration-response curves, that allowed estimating the IC50 values. The affinity to the H3R was assessed through binding assays and the Ki values were then calculated. Results: The designed compounds were synthesized with yields up to 67%. Of these, despite the low affinity shown at both cholinesterases, two compounds showed measurable inhibition at AChE. On the other hand, six compounds showed considerable affinity at the H3R, with compound LINS05a123 being highlighted due to its submicromolar affinity (pKi = 6.27). This compound also showed selectivity towards AChE (IC50 = 198 µM). Compound LINS05c214 is also highlighted due its higher inhibitory potency at AChE (IC50 = 112 µM) and considerable affinity at the H3R (pKi 5.83), being the most interesting by considering the multitarget proposal. The results suggest that longer linker groups along with pyridylpiperazine as basic motif contributes to the observed activity at both targets. Conclusions: The data obtained provide important information that will help in the development of further multitargeted compounds.

Expression of cathepsins B, L, and S and the activity of dipeptidyl nitrile derivatives in pancreatic and liver cancer cells

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Pancreatic and liver cancers have a high mortality rate and occurrence of metastasis. Chemotherapeutic agents are usually applied in this case but are of limited use. Therefore, novel therapeutic alternatives are needed, and cysteine protease inhibitors constitute an option as a standalone or combination therapy. Cathepsins B, L, and S are involved in neoplastic processes and are targets for reversible covalent inhibitors. Among different types of cathepsin inhibitors, dipeptidyl nitrile derivatives have been studied for cancer types. In this work, the aim was to identify bioactive chemicals from a series of fifteen dipeptidyl nitrile derivatives based on a previous bioactive chemical (coded Neq0780) against pancreatic (MIA PaCa-2) and liver (HepG2) cancer cell lines in contrast to non-tumoral fibroblast (Balb/3T3 cone A31) cells. In addition, the expression of the three cathepsins mentioned and found in the literature as responsible for processes such as tumor progression was determined for cancer cell lines. The MTT assay was used to assess the viability/cytotoxicity of the compounds after 72 h incubation of 1.0x10^5 cell/well in 96-well plates. Then, the combined therapy test was also carried out with the precursor compound (Neq0780 at 10 μM) to verify whether it has a synergistic effect when combined with a set of concentrations for the reference chemotherapy (gemcitabine and doxorubicin). The analysis of the cathepsin expression was performed using the Western Blot method, using a 15% polyacrylamide gel for the electrophoresis step, where the bands were labeled using specific primary and secondary antibodies quantified by chemiluminescence. As expected, no compound showed cytotoxicity against tumor cells alone or in combination therapies. The Western Blot assay allowed us to identify that there are three cathepsins (L, B, and S) expressed in the pancreatic cancer line MIA PaCa-2. However, in the HepG2 hepatic tumor cell line, only cathepsin L was expressed and in low concentration. These results demonstrate that the cancer cells express at least one type of cathepsin. Still, known inhibitors were inactive in cells showing that (i) these chemicals may not be targeting the intracellular enzyme, or (ii) the cells can still survive despite the enzymatic inhibition provided by these chemicals. Functional studies to evaluate the cathepsin activity inside the cells are now being undertaken to understand the lack of activity.

Combination therapy assays with doxorubicin and cathepsin L inhibitors against the triple-negative breast cancer line MDA-MB-231

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Breast cancer, characterized by its aggressive potential and high metastatic capacity, is a worldwide health problem for the female population. Consequently, chemotherapies are applied to control de development of the disease, including doxorubicin, a reference drug currently used for triple-negative breast cancer cells. Cathepsin L is a cysteine protease highly expressed in many tumors, where novel dipeptidyl nitrile inhibitors have been designed and studied over time in our research group. Therefore, this study used a combination of 12 novel cathepsin L inhibitors with doxorubicin against the triple-negative human breast cancer cell line MDA-MB-231. The cells were cultivated using DMEM medium supplemented with 10% FBS maintained in an incubator at 5% CO2 and 37 ºC. Compounds were added to 96-plates at a concentration of 1.0x105 cells/well. After 24 h incubation, the medium was removed to add 10 µM cathepsin L inhibitors and a range of doxorubicin concentrations (1.0-1 nM). The system was incubated for 72 h, being subject to MTT assay. The Bliss test was used to evaluate the concentration-dependent assays, which led to synergism for many chemicals. The results showed that the best synergism effect improved doxorubicin potency by 15-times more than its standalone administration. The molecular mechanism is now under study to understand the combination effect. This work proved that the combined therapy was also selective against the triple-negative breast cancer cell line once the cytotoxicity was reduced for the non-tumoral cell line BALB 3T3 clone A31.

Acetylsalicylic acid reduces skin inflammation caused by UV irradiation: Role of the 15-epi-lipoxin A4 – ALX/FPR2 axis

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Background: Targeting the physiopathological mechanisms of UV irradiation-induced skin inflammation is a promising approach to reduce skin damage. Lipoxins and aspirin-triggered lipoxins (AT-LXA4) are mediators generated during inflammation that elicit anti-inflammatory and pro-resolution bioactions by binding to a high-affinity, G protein-coupled lipoxin A4 (ALX)/formyl peptide receptor (FPR2). Objectives: To determine if the effect of acetylsalicylic acid (ASA) would be inhibited by BOC-2 (an ALX/FPR2 receptor antagonist) indicating the dependence on AT-LXA4, and then if AT-LXA4 would mimic the ASA activity on the inflammatory response induced by UV in mice. Methods: Inflammation in the skin of hairless mice were determined after UV irradiation (4.14 J/cm2). Results: Pretreatment with ASA and AT-LXA4 ameliorated the signs of UV-induced inflammation by reducing neutrophil recruitment, and mast cell counts, that led to decrease in collagen degradation, sunburn cells formation, decrease in pro-inflammatory cytokines levels (tumor necrosis factor-α [TNF-α], interleukin [IL]-1β and IL-6), and increase in anti-inflammatory cytokines (transforming growth factor [TGF]-β and IL-10). All effects were abrogated by BOC-2. Thus, ASA mechanism to inhibit UV-induced skin injury in hairless mice depends on AT-LXA4 action on ALX/FPR2 receptor, since the effects of ASA were mimicked by AT-LXA4, and BOC-2, an ALX/FPR2 antagonist, inhibited the effects of ASA and AT-LXA4. Conclusions: AT-LXA4 is involved in the beneficial effect exerted by ASA on UV-induced skin injury and AT-LXA4 action on ALX/FPR2 receptor explains the modulation of inflammatory parameters by ASA in UV skin inflammation further contributing to understand ASA therapeutic applicability in UV irradiation skin pathology scenario. Furthermore, AT-LXA4 are promising candidates as therapeutic agents against UV-induced skin inflammation.

In vitro evaluation of in silico repositioned drugs against Mycobacterium tuberculosis

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Background: According to the latest report published by the World Health Organization, Tuberculosis (TB) is still one of the top leading causes of death worldwide. Moreover, multidrug-resistant and extensively drug-resistant strains have been rising over the decades. Therefore, new MTB drugs are highly needed. The in silico screening method can be applied to develop and also repurpose pharmaceutical drugs to aid the TB scenario. Objectives: Perform in vitro assays for six in silico repurposed drugs, namely Orlistat (ORL), Carvedilol (CAR), Otilonium Bromide (OTI), Ketoconazole (KET), Daclatasvir (DAC) and Lomitapide (LOM) against three MTB strains, H37Rv, Erdman and CDC1551. Analyze each individual inhibition potential and synergistic profile with standard TB drugs. Evaluate the in silico proposed mechanism of action. Methods: Microplate Alamar Blue Assay (MABA) was used to identify the Minimum Inhibitory Concentration (MIC) for all drugs, including the standard treatment Isoniazid (INH), Rifampicin (RIF), Ethambutol (EMB), Delamanid (DEL) and Bedaquiline (BED). Fractional Inhibitory Concentration Index (FICI) was used to analyze synergism, no-effect or antagonism. Thin layer chromatography (TLC) was used to check for mycolic acids inhibition. Results: The MICs for each individual drug were as follow: ORL 12.5-25, CAR 6.25, OTI 12.5-25, KET 50-100, DAC >100 and LOM 50-100 µM. The drugs with the lowest MIC (ORL, CAR and OTI) were selected for the FICI assay. Synergism was identified for the combinations: ORL/BED (0.3125), ORL/RIF (0.3125), CAR/BED (0.3125), CAR/RIF (0.3125) and OTI/BED (0.5). The TLC assay demonstrated that ORL has an inhibition profile similar to INH, which could indicate at least one of its mechanisms of action. Conclusions: The in silico screening identified three compounds with the potential for repurposing (ORL, CAR and OTI), with all three demonstrating low in vitro MICs against the strains and synergism with at least one drug from the standard TB treatment. More studies are needed to further determine its mechanisms of action and whether the repurposed drugs can maintain its activity in vivo.

Effects of novel urease inhibitors on major virulence factors and growth of Cryptococcus spp.

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Cryptococcus spp. is a yeast with clinical relevance for causing cryptococcosis, a systemic mycosis that mainly affects immunocompromised individuals with high mortality rates. Some virulence factors are associated with the establishment of the infection and the urease enzyme is used for the spread of the fungus mainly to the central nervous system. Considering that urease is naturally absent in humans, enzyme inhibition may be an interesting strategy in the treatment of cryptococcal meningitis, especially in association with conventional antifungals. In view of this, some synthetic molecules of new chemical classes were tested to control fungal growth and virulence factors of *C. neoformans* and *C. gattii*. A lead compound (AF19) was chosen considering its inhibitory activity on fungal growth of 14 strains at 2-8 µg/mL using the broth microdilution technique. Therefore, AF19 was also tested against urease activity, biofilm formation, capsule enlargement, and titan cell formation. AF19 was able to inhibit urease activity at low concentrations from 0.5 to 1 µg/mL, in addition to action against biofilm formation at 128 µg/mL and inhibiting the growth of cells in the dispersion of mature biofilm at 2 µg/mL. Furthermore, the treatment of yeasts with subinhibitory concentrations of AF19 was able to significantly reduce the capsule thickness and inhibit the formation of titan cells. The data obtained indicate a great potential of AF19 in controlling some virulence factors of Cryptococcus spp. and may be a promising strategy for the study of new potential antifungals.

Molecular Modeling of Crystal Polymorphism and Potential Co-Crystal Design of Drug Macitentan

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Macitentan is a dual endothelin receptor antagonist used in the treatment of pulmonary arterial hypertension to delay disease progression approved in 2013. However, low water solubility hampers reproducible bioavailability after oral administration. Thus, the study of their crystal structures contributes to a better understanding with other molecules of interest (co-crystals) and can provide a modified final product with an improved therapeutic profile. The general objective of this project is to design new macitentan co-crystals, aiming to indicate the most promising co-crystal for development of a more effective crystalline molecular complex in terms of drug solubility. Molecular modeling and computational chemistry methods were employed in order to propose the most promising macitentan co-crystals. Mercury, Avogadro and MOPAC programs was used in the initial screening of potential co-formers. Molegro Virtual Docker program was used to refine the screening of coformers by applying molecular docking. 37 candidate molecules as co-formers were found by qualitative screening. However, all coformer molecules were quantitatively evaluated, using the molecular docking approach, to define an energy ranking and data analysis. The ranking of interaction energies between macitentan and co-formers indicates that only six compounds are the most promising, they are maltitol, L-glutathione, riboflavin, pamoic acid, hesperetin and thymidine. The most stable and promising macitentan co-crystal crystalline systems will be rationally proposed for future crystallization and dissolution studies.

Applying machine learning in drug repositioning of FDA-approved drugs for identifying a potential antiplatelet candidate

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Background: Thromboxane A synthase (TXAS) is the enzyme responsible for synthesizing TXA2, a potent platelet aggregating that plays a vital role in thrombotic events. Virtual screening (VS) using molecular docking is a helpful tool for identifying putative inhibitors for several targets through scoring functions to predict the ligand-protein binding affinity. In this context, machine learning algorithms enable to obtain classification models to improve the ranking of potential compounds by molecular docking. Objectives: Identify putative TXAS inhibitors (TXASI) among FDA-approved drugs by a machine learning classification model based on molecular docking and physicochemical properties of ligands. Methods: ChemBL database was used to search TXASI. After removing duplicated structures, inorganic salts, and undefined stereoisomerism, two sets were considered to 144 compounds each: active set (pIC50 ≥7.3) and inactive set (pIC50 ≤7.0). We used the following programs: Open Babel to generate the structures (pH=7.8); GOLD to perform the molecular docking; DataWarrior for physicochemical properties; and KNIME to develop the classification models. The datasets were normalized, filtered by linear correlation, and partitioned in the training and test sets (70:30). The tenfold internal cross-validation was carried out with Extreme Gradient Boosting (XGBoost). The model containing the best metrics was used for the VS in an external dataset with 2736 FDA-approved drugs. Results: The ChemPLP classification model with stratified random partition mode showed the best metric of receiver operating characteristic curve (AUC-ROC=0.82), Matthew's correlation coefficient (0.49), and F1 (0.74), with a recall of 74% of actives, 75% of inactive and accuracy of 74%. The prediction for all compounds in the test and FDA datasets was considered reliable. Our results predicted that 85 drugs from the FDA dataset would be active as TXASI, of which the antimicrobial gatifloxacin showed the best performance (P=0.86). Conclusions: We use machine learning classification models in the VS of FDA-approved drugs. The results indicated gatifloxacin as a putative TXASI for drug repositioning candidate as an antiplatelet.

Synthesis and cytotoxic activity of 1,2,3-triazole-4-methylcoumarin hybrids

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Background: Cancer is a leading cause of death worldwide. Coumarins have shown a variety of anticancer activity, and triazole is commonly used in medicinal chemistry as a ligand, linker or for its own activity. Objectives: Synthesis of 1,2,3-triazole-4-methylcoumarin hybrids LaSOM 180, 185, 186 and 190 using umbeliferon as precursor and test their antitumor activity and in vitro toxicity and selectivity index (SI). Methods: The coumarins were obtained using Pechman and Huisgen reactions which lead to the hybrids with good yields and purity. MTT and Neutral Red assays were performed on A549 (lung cancer), HepG2 (liver cancer), J774A1 (mouse sarcoma macrophage), MCF7 (breast cancer), OVACAR (ovarian cancer), RAW (murine leukaemia macrophage), Siha (uterus carcinoma) and 3T3 (healthy fibroblasts) cell lines. Results: Potent antitumor activity was showed across all cell lines, but especially against MCF7 breast cancer cell line, where all compounds had IC50 between 2.66 and 10.08 μM, lower than that of the reference drug cisplatin (45.33 μM). LaSOM 186 had an IC50 lower than 100 μM on all cancer cell lines it was tested on except cervical carcinoma Siha. LaSOM 185 also had potent activity on HepG2 liver cancer cell line (IC50 88.29 μM), and LaSOM 190 on J77A1 mouse sarcoma macrophage (33.04 μM), besides both of them on MCF7 (5.04 and 2.85 μM, respectively). Their IC50 on 3T3 healthy cell line ranged between 0.62 and >40 μM, against cisplatin's 5.90 μM. All of the molecules' SI for MCF7 breast cancer cell line, with values between 0.23 and 7.93, were greater than that of cisplatin 0.13. Conclusions: All triazole-coumarin compounds showed potent activity among the used cancer cell lines with better selectivity than the reference drug cisplatin. We are performing tests for mechanism elucidation.

Synthesis and biological evaluation of new antipasitary agents containing the 1,2,4-oxadiazole core

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Background: Recently, our research group synthesized new hybrid derivatives from vinyl-1,2,4-oxadiazoles (VOD) and substituted isatins, through the Morita-Baylis-Hillman (MBH) reaction. Some of these substances showed good antiparasitic activity against *Trypanosoma cruzi* and *Leishmania infantum*. Based on these promising biological results, it was planned to obtain aza-MBH analogues of these adducts using the hybridization strategy between VOD and *N*-Boc imines from isatins, since the biological evaluation of these new substances will allow a structure-activity relationship study. Objectives: This work aims at the synthesis of new aza-MBH adducts containing the 1,2,4-oxadiazole core and its biological evaluation against *T. cruzi* and *L. infantum*. Methods: The aza-MBH adducts were obtained from the reaction of VOD (1.1 eq.) and *N*-Boc imine (1 eq.) in acetonitrile (0.1M) at room temperature, using DABCO (1.05 eq.) as base and acetic acid (1.05 eq.) as catalyst. The biological evaluation was performed by the Laboratory of Medicinal and Computacional Chemistry, USP-São Carlos. Results: So far, two aza-MBH adducts were obtained, with yields of 62% (**A**) and 87% (**B**). Adduct **A** showed IC50 *T. cruzi* = 24.72 µM and IC50 *L. infantum* = 29.04 µM, while adduct **B** showed IC50 *T. cruzi* = 22.18 µM and IC50 *L. infantum* > 64 µM. **A** and **B** showed CC50 *HFF-1* > 64 µM. Both aza-MBH adducts are less potent than their MBH adducts analogues previously obtained, which showed the following antiparasitic activity: **A'** - IC50 *T. cruzi* = 2.20 µM and IC50 *L. infantum* = 3.73 µM; **B'** - IC50 *T. cruzi* = 2.30 µM and IC50 *L. infantum* = 7.28 µM. Conclusions: The results of the biological evaluation of the two new 1,2,4-oxadiazole derivatives indicated that the hydroxyl group is responsible for a better antiparasitic activity than the *N*-Boc imine group. New structural modifications are being planned in order to carry out a broader structure-activity relationship study. Acknowledgements: We thank FAPESP (grant 2021/13544-5 and 2003/07600-3), CNPq (grant 151763/2022-4 and 301330/2018-2) and CAPES for scholarships and financial support.

Catalytic Function Aspects of CD73 by Computational Studies

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Background: Recent findings show a tumor-induced immunosuppressive mechanism, whereby CD73 in the tumor microenvironment produces extracellular adenosine, which promotes tumor growth by limiting T-cell antitumor immunity via adenosine receptor signaling. For this reason, research and clinical trials of new CD73 inhibitors have been increasing in recent years. The CD73 N-terminal domain coordinates the binding of two catalytic zinc ions, while the C-terminal domain provides the binding pocket for AMP. This process requires a large lateral rotation of the N-terminal domain to expose the substrate-binding site. Objectives: The protein-ligand binding involves a complex recognition process. For this reason, we use molecular dynamics (MD) simulations with other in silico tools to understand CD73 mobility and the dynamic CD73 recognition pathway, to help in the molecular design of new CD73 inhibitors. Methods: Domain motion analysis was performed using the DynDom web server. The graphical user interface LiGRO was used to run the molecular dynamics. LiGRO used the program ACPYPE and GROMACS to build input files for the complex and run the simulations. Results: The results obtained by the DynDom server, showed that more residues may be involved (327-338). In addition, the DynDom server also shows that the range of motion can reach an angle of 115.12º, a little more than what was described by Knapp (114º). The MD of unbounded CD73 showed that the greatest fluctuations occurred on the C-terminal domain (residues 335 to 547), as regards the macromolecule's mobile domain. This fact corroborates with the information described by Knapp and colleagues, which stated that the rotation movement of the C-terminal domain seems to be a realistic situation when the CD73 is in solution because the movement of the C-terminal domain around its center would require much less displacement of water molecules. Conclusions: The large movement of CD73 domains makes the use of structure-based virtual screening difficult. This work showed the different variations in the open and close movement of CD73 to help the small molecule CD73 inhibitor activity discovery process.(CNPq/CAPES)

Design and synthesis of selective MAO-B inhibitor based on the safinamide structure

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Alzheimer's disease (AD) is a neurodegenerative disorder associated with the intellectual memory loss and other cognitive impairments. The exact cause of progressive neuronal degeneration in AD is not known. However, etiology of the disease is linked with the presence of oxidative stress and MAO-B hyperactivity in gliosis which increases the levels of hydrogen peroxide and oxidative free radicals. High levels of MAO-B also contribute to the production of amyloid-β plaques. In preclinical studies, it has been found that MAO-B inhibition can cause cognitive improvement. Therefore, use of more selective and effective MAO inhibitors can be an additional target for AD. Objective: Through rational drug design, modulate a new selective MAO-B inhibitor analog from the safinamide drug molecule, aiming pharmacodynamic and pharmacokinetics improvement for use in Alzheimer's disease. Method: The safinamide´s analog molecule was proposed from the conjunctive approach of expanding the rational planning of new drugs and submitted to the prediction of physicochemical and pharmacokinetic properties by the SwissADME software. Pharmacodynamics was analyzed from molecular docking using two different softwares Autodock Vina and GOLD using 2V5Z crystallographic structure from Protein Data Bank (PDB). The novel safinamide analog molecule was synthesized in the lab with a simplified route and high yield. Results: In silico pharmacokinetic studies suggest that the new molecule is safer than safinamide, demonstrating a set of more favorable characteristics for good bioavailability. Through the molecular docking study, the planned compound showed a greater affinity for the MAO-B enzyme than safinamide, demonstrating a positive result for optimization. The organic synthesis of the analog in the lab demonstrated a yield of 74%, demonstrating a high potential for scale production. Conclusion: With the molecular docking results obtained, we can have great perspectives regarding the optimization of the safinamide molecule by the synthesis of the new compound. In addition, the synthetic route has proved to be simple and profitable. Acknowledgment: Fapesp 2018/02879-3, Faepex-Unicamp 2559/20 and CAPES—Finance Code 001

Docking-based molecular optimization of new N-heterocycles designed for PI3Kδ inhibition

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Background: The class I phosphoinositide-3-kinase (PI3KC1) is a lipid kinase family enrolled in cell signaling and that may be a therapeutic target in cancer diseases, among others. The first FDA-approved PI3Kδ-selective (idelalisib) exhibits a propeller-shaped conformation on the active site, which confers great selectivity over isoforms δ and/or γ. In this work, we design new molecules structurally related to idelalisib that present the N-heterocycles pyrazolo[3,4-b]pyridine and pyrazolo[1,5-a]pyrimidine nuclei. The planned molecules must have the desired propeller-shaped, be able to perform hydrogen-bond interactions (HBI) with two key residues of the hinge region (Glu826 and Val828), and have adequate values of lowest binding energy (LBE). Objectives: Design N-heterocyclic molecules, structurally related to idelalisib, leading to high-affinity ligand-PI3Kδ enzyme interactions. Methods: The structures of the N-heterocyclic derivatives were based on the bioisosterism concept. The new molecules designed were evaluated against the PI3Kδ enzyme (PDB-ID: 6G6W, R = 2.72 Å) using the molecular docking method with the Autodock 4.2 program, previously validated by the redocking protocol. The intermolecular interactions between putative inhibitors and PI3Kδ were evaluated with BIOVIA Discovery Studio Visualizer 2020 program. Results: To enhance the HBI profile, we change the substituents at C-4 and N-1 from the N-heterocycle nuclei. The changes led to the proposal of 20 new molecules, which we submitted to molecular docking simulations. We selected 4 out of them that showed at least 2 HBI with one of the two targeted amino acid residues, with 3 among them interacting with both. The selected molecules had lower values of LBE (-9.69 to -10.95 Kcal/mol) than idelalisib's (-9.54 Kcal/mol). Conclusions: The results indicate an improvement in the design molecules compared to the previous studies, showing the usefulness of the molecular docking technique in the planning and optimizing potentially bioactive compounds. The optimized molecular structures are being synthesized to be evaluated biologically. Acknowledgments: To FAPERJ, CAPES, and UFF for financial support. We also thank FAPERJ for scholarships (E-26/201.163/2020 and E-26/201.133/2020).

To target and decrease the myeloid-derived suppressor cells (MDSCs) population through the treatment of low-dose chemotherapy with cyclophosphamide and 5-fluorouracil

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Introduction: The immunosuppressive tumor microenvironment represents the key factors stimulating tumor progression. Immunosuppression was found to be associated with chronic inflammatory mediators including cytokines, chemokines, and growth factors produced by cancer and stroma cells. Long-term intensive production of these factors induces the formation of myeloid-derived suppressor cells (MDSCs) representing one of the most important players mediating immunosuppression and leads directly stimulating tumor growth and metastasis. Objective: To develop a tumor mice model through induction of 4T1 breast cancer cell lines and apply low-dose chemotherapy to target and decrease the myeloid-derived suppressor cells (MDSCs) populations through the treatment with cyclophosphamide and 5-fluorouracil anti-cancerous chemotherapeutic agents. Methodology: Female BALB/c mice (20 ± 1 g, body weight) were obtained from the UFG, by CEUA approval. Five groups of five mice in each group were divided among them; three groups were developed as tumor-bearing. A tumor model was developed by inducing 4T1 cell suspension at 4x105 cells/ml. Four days of continuous treatment of cyclophosphamide (80 mg/kg) and 5-fluorouracil (80 mg/kg) were given. The tumor size and growth were measured by Lumina using the luciferase enzyme and analyzed. The statistical significance of the differences was analyzed by t-test or one-way analysis of variance. The value of p < .05 was considered significant. Results: significant weight growth and volume have been observed in the treatment groups compared with positive control of the animal during the treatment period. Alone, treatment of 5-fluorouracil reduced the tumor average growth rate, while thoracic metastasis average growth has been reduced compared to the positive control group. The co-relation of white blood cells with the spleen is analyzed in linear regression, which shows the variable difference with impairment of cells. Conclusion: the following treatments with 5-fluorouracil chemotherapeutic agents have shown a reduction in tumor size and both cyclophosphamide and 5-fluorouracil in the thoracic metastasis compared to the positive control group. The white blood cells have been impaired in the treatment groups of cyclophosphamides and 5-fluorouracil. Immunosuppression has been observed by impairing white blood cells and their subsets.

Selenium compound shows antifungal effect on Cryptococcus gattii and interferes on its virulence factors

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Cryptococcus gattii is an ethological agent of cryptococcosis and several virulence factors are responsible for the infection establishment highlighting the increased capsule, titan cells formation, and melanin production. There are few available antifungal and resistant strains are emerging leading the prospection of new molecules with potential antifungal. Then, this study aims to evaluate the action of a new compound (LQA_78) on *C. gattii* and its virulence factors. The broth microdilution technique was performed to determine the minimum inhibitory concentration (MIC) of ampothericin B (AMB), fluconazole (FLC), flucytosine (5-FC), and LQA_78 against a standard strain (R265) and clinical isolates (n=5). The morphotypes normal cell with enlarged capsule thickness (NcC) and titan cell (Tc) were induced in vitro using specific mediums and both cells were also submitted to LQA_78 susceptibility testing. After treatments, cell morphometry, determination of capsular permeability using fluorophore rhodamine isothiocyanate-dextran and plasma membrane by DNA and protein quantification were performed. For melanization assay the yeasts were cultivated on minimum medium containing L-DOPA without or with LQA_78 . *C. gattii* strains were susceptible to AMB (0,125-1µg/ml) and 5-FC (0,5-1 µg/ml) but reduced susceptibility to FLC (2-32 µg/ml). LQA_78 showed inhibitory effect on *C. gattii* strains (1-64µg/ml) and similar data were obtained for both morphotypes. In addition, LQA_78 led a reduction of capsule and plasma membrane permeability due to greater cell fluorescence and DNA/proteins amounts. Treatment with LQA_78 also promoted the inhibition of melanin production in *C. gattii* . Our data demonstrate that the LQA_78 presented an inhibitory and fungicide action on *C. gattii* and its morphotypes and highlight the potential of the compound to act directly on the virulence factors responsible for the tolerance of *C. gattii* during the pathogenesis of cryptococcosis opening new paths of research to be followed such as in vivo models and improvement of the compound.

In silico study of a new synthetic thiophenic amide (E)-N- (4-methoxyphenethyil)-3-(thiophen-2-yl)acrylamide as a possible vasorelaxant drug

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Background: (E)-N-(4-methoxyphenethyil)-3-(thiophen-2-yl)acrylamide (MFTA) is a new synthetic thiophenic amide in which the furan ring oxygen has been replaced by sulfur creating a new molecule. Objectives: Considering that MFTA showed in vitro vasorelaxant activity in rat aorta, we decided to carry out a theoretical study of molecular docking (MD) investigating possible targets of this relaxing pathway. Methods: MFTA was drawn using the program ChemBioDraw Ultra 12.0 and submitted to MD in Molegro Virtual Docker v.6.0.1, using M1, M3, CB1 receptors; phosphodiesterase 4; Rho-cinase (ROCK-1) and transient receptor potential cation (TRPV4); voltage-gated sodium and calcium (Cav1); potassium channels obtained from Protein Data Bank, taking as reference the energy value of the MolDock and Rerank Score algorithms (kcal/mol), respectively. Results: from the nine proteins analyzed only four showed more negative energies for the amide compared to the control drug. Therefore, for the M1 receptor, more negatives results were obtained from MFTA (-107.1 and 86.8), when compared to the control drug (-105.7 and-92.7), indicating that MFTA was able to make more strong bonds, including 8 hydrogen, in addition to 5 hydrophobic and 4 steric, while the control drug only performed two types of interaction. For ROCK-1 the results were also more negative for the MFTA (-78.6 and -60.6), due to more types of interaction, a hydrogen bond in the aromatic ring, 3 hydrophobic and 3 steric, even though control drug (-76.8 and -73.3) made more strong bonds, 6 hydrogen, in addition to 3 hydrophobic. As for the Cav1, MFTA was shown to require less energy (133.0 and -111.6), which can be linked to its ability to perform more hydrogen bonds, 7 bonds, in addition to 6 hydrophobic, while the control drug (-81.8 and 123.0) only performed 6 hydrogen and 2 steric. Finally, the potassium channel also showed better affinity for MFTA (-133.0 and -112.9), which can also be explained by the greater number of stronger bonds performed, 5 hydrogen, 5 hydrophobic and 1 steric, while the control drug (-103.0 and -75,7) performed 6 hydrogen, 4 hydrophobic, and 2 steric. Conclusions: M1, ROCK 1, Cav1 and potassium channels are possible targets for the vasorelaxant effect of MFTA.

Trypanocidal effect of a novel trimetoxiphenylchalcone against Trypanosoma cruzi strain Y in vitro

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Chagas disease (CD) is caused by *Trypanosoma cruzi* and affect 6 to 7 million people worldwide. Beznidazole is the main drug available for treatment, and possess low efficacy on the chronic phase and high toxicity. Recently, our group has been studying the effect of several synthetic and semi-synthetic chalcones on the lifeforms of *T. cruzi*, with interesting results. In this way, this work aimed to study the effect of the synthetic chalcone (2E,4E)-1-(2-hydroxy-3,4,6-trimethoxyphenyl)-5-phenylpenta-2,4-dien-1-one (Chalc1) on *T. cruzi* strain Y in vitro. Epimastigote forms were incubated with Chalc1 (1000-62.5 µM) in 10% FBS LIT medium and the viable parasites were counted after 24 hours. The concentration able to inhibit 50% of epimastigote proliferation (IC50) was estimated by nonlinear regression. The trypomastigotes were obtained from the supernatant of infected LLCMK2 cells and incubated with Chalc1 for 24 hours. The effect was evaluated by counting on Neubauer chamber. The percentage of viable cells were used to estimate the LC50 (concentration able to kill 50% of trypomastigotes). On both experiments, untreated parasites were used as negative control and Benznidazole (1000-62.5 µM) was used as reference drug. All experiments were performed in triplicate, with n=3. The data was presented as mean ± standard error mean, and the comparison was performed using Anova with Dunnet's posttest, using p<0.05 as significance criteria. Chalc1 was active against both epimastigote and trypomastigote forms, with antiparasitic effect higher than benznidazole. Chalc1 showed LC50 and IC50 values of 63.4 ± 17.3 µM and 43.1 ± 5.7 µM, while Bz displayed 161.4 ± 31.8 µM and 115.1 ± 16.3 µM, respectively. In conclusion, the synthetic chalcone (2E,4E)-1-(2-hydroxy-3,4,6-trimethoxyphenyl)-5-phenylpenta-2,4-dien-1-one presents trypanocidal effect and can be further investigated as candidate for the development ok antichagasic drugs.

THEMATIC AREA:

Food and Cosmetical Technology

Patent applications from 2015 to 2021 that use fruit residues in methods of extraction and prepare processed foods and beverages

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The United Nations Environmental Program has estimated a total of 931 million tons of global food waste per year in 2021. This large loss contributes to reduced sustainability and food insecurity. Necessary measures need to be taken to reduce food waste and governmental and non-governmental bodies are expressing strong concern regarding this subject. Fruit residues such as peel, bagasse, and seeds can be used as a functional food and promote health benefits, focusing on this aspect, several countries contributed with technologies, by using fruit residues in processed foods or improving industrial processes. The objective of the present work was to identify patents that use fruit residues as functional foods, evaluating the benefits to human health, and analyzing the use and application in the Food and Beverage industry. The initial screening considered 321 patents by searching through the Espacenet Patent database using the keywords 'fruit' and 'residue' in the title or abstract. 52 patents were excluded for being replicas, and unavailability of access, totaling 269 available. Inclusion criteria were adopted, such as type of fruit residue used, fruit residue as the main ingredient, and functional health claims. Thus, 209 patents were excluded and a total of 60 patents were accepted. China was the country with the most technologies (33 patents), followed by the United States (8 patents). Twenty-seven different types of fruit were found, where the residues were used to assist in the preparation of industrialized foods, food additives, and processing methods. The patents most used fruit residues were citrus species (24 patents) and passion fruit (5 patents). In addition to identifying 15 different types of health benefits, such as antioxidant activity (22 patents), improvement of gastrointestinal functions (15 patents), cardioprotective properties (11 patents), and anticancer activity (9 patents). In conclusion, researchers and industries have great interest in the patents since fruit residues are considered functional foods with reported health benefits and are a sustainable alternative. The analyzed patents contributed significantly to the reduction of food waste, attributing applicability to the food industry.

Photoprotective and antioxidant potential of new synthetic UV filters derivative

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UV radiation can lead to the generation of reactive oxygen species (ROS), which damage lipids, proteins and DNA. UV filters do not completely block solar radiation, and most of them only absorb in the UVB range; some UV filters may also show instability when exposed to the sun; consequently, there is a search for new more photostable compounds and for combinations of UV filters with photostabilizers and antioxidant substances, aiming to minimize the UV-induced effects on the skin such as directly UV damage or even the ones resulting from ROS formed during the process. Therefore, this study evaluated photoprotective and antioxidant potential of a resveratrol's derivative, obtained by a new strategy of molecular triplication, using *in vitro* models of monolayers and reconstructed human skin. Phototoxic potential was evaluated according to the OECD TG 432 using fibroblasts monolayers and the antioxidant activity was conducted using the DCFH2-DA probe both in keratinocytes monolayer model and *in house* reconstructed human skin model. Firstly, the derivative showed absorption in the UVB (280 – 320nm) and UVA II (320 – 340nm) range and photostability, with a lower UV absorption decrease. Also, it did not show phototoxicity potential (MPE values lower than 0.1). Regarding the antioxidant activity, all derivative's tested concentrations (31.25 - 1000µg/mL) did not protect against UVA-induced ROS production in keratinocytes monolayers model. The study performed in reconstructed human skin model did not show a significant reduction of UVA-induced ROS production (3%), when the compound was tested at 500µg/mL. So far, this study showed that new strategies with resveratrol's structure modifications were able to generate a broad spectrum, non-phototoxic and more photostable derivative. Also, it can be encapsulated in a nanoparticulate system and/or combined with UV filters and antioxidant compounds to increase the photoprotective potential.

Evaluation of Brazil-nut residues as an antioxidant ingredient for sunscreen formulation

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Residues of Amazonian fruit such as Brazil nut shells are frequently discarded but with their antioxidant potential may be used as a sustainable cosmetic active ingredient. However, their efficacy and photosafety should be guaranteed. This study evaluated phototoxic and antioxidant potential of Brazil nut shells extract (BNE). BNE was obtained by maceration during 72h with acetone: water (7:3). Then, its fractionation was performed with hexane, dichloromethane, ethyl acetate and butyl alcohol. The absorption spectrum and photostability of BNE and fractions were analyzed by spectrophotometry. Phototoxicity was evaluated in fibroblasts (3t3) monolayer (OECD TG 432) and 3D reconstructed skin model. The ocular irritation potential was evaluated by HET-CAM assay. Also evaluation of protective effect against UVA-induced ROS production in fibroblasts (3t3) monolayers and 3D reconstructed skin model using DCFH2-DA probe were performed. Ethyl acetate fraction (F3) of BNE presented higher absorption in the UVB region and was selected for the other assays. F3 was considered photostable with photodegradation of 0,9% at UVA region, and photodegradation of 0,1% at UVB region. For phototoxic assay in monolayer, F3 presented phototoxic potential (MPE>0.15). Nevertheless, when F3 was tested for phototoxicity in 3D skin model, it did not present any phototoxic potential. It also did not show ocular irritation potential. F3 presented good protective effects against UVA-induced ROS production in fibroblasts monolayers in the range of 31.25-500µg/mL and also decreased free radical production in 3D skin model when used at 200µg/mL (about 47% of reduction). Thus, this study showed that reusing fruit residues may be an interesting strategy for the application of a sustainable raw material in cosmetic formulations. Since F3 was considered photosafe and nonirritant in 3D skin model and HET-CAM assays, respectively, and it showed good antioxidant properties evaluated not only on fibroblasts monolayer, but also on 3D skin model. F3 may be a suitable ingredient to be combined with UV-filters due to this antioxidant activity and photosafety.

Development of a nanodelivery system for lytic Psg phage particles: potential for the biocontrol of coffee plant bacterial blight

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Brazilian coffee production has been strongly affected by phytopathogenic bacteria that cause bacterial canker/blight and lead to serious economic losses. The use of pesticides, copper and antibiotics in crops negatively impacts food safety and the environment. The aim is to use green technology via development of a nanoparticle formulation using lytic bacteriophages to eliminate bacteriosis caused by the phytopathogen Pseudomonas syringae pv. garcae (Psg). A simple coacervation method was used for the production of chitosan nanoparticles with encapsulated phage particles, together with a factorial design to optimize the process conditions that allowed to obtain the best particle size. Concentration, pH and agitation time parameters were the parameters optimized. Nanoparticles of alginate coated with 0.3% (w/w) chitosan were prepared by dissolving chitosan (30 mg) in ultrapure water (10 mL) containing 100 µL of acetic acid, under continuous magnetic stirring for 24 h, after which the resulting mixture was vortexed and sonicated for 30 min, and pre-established concentrations of $CaCl_2$ were added. The resulting solution was centrifuged at 10000g and pH of the supernatant adjusted to 5.5 with NaOH (1M). The final solution was filtered (0.45 µM pore size filter) and stored at 4 °C. The nanoparticles were analyzed for hydrodynamic size, Zeta potential and polydispersity index via Dynamic Laser Light Scattering, morphology by scanning electron microscopy and evaluation of the maintenance of phage particle lytic viability following nanoencapsulation. Nanoparticles were thus obtained capable of carrying and fully stabilizing whole phage structures, while maintaining their lytic activity during ex vivo and in planta bacterial inactivation assays, attaining more than 4-logs of bacterial reduction. Hence, one may conclude that the use of nanoencapsulated lytic phages have the potential to help in the fight against Psg-induced bacterial blight in coffee farming, contributing to the reduction of environmentally aggressive compounds in favor of both food safety for consumers and sustainable growth in a highly globalized market.

Profile of formulations for the prevention/treatment of skin aging in a compounding pharmacy in the city of Vitória-ES

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Introduction: the concept of beauty follows standards in which the youthful appearance of the skin is extremely valued. However, skin aging is a natural process that occurs due to intrinsic (genetic, hormonal) and extrinsic factors (solar radiation, pollution, poor diet), which result in manifestations such as sagging, wrinkles, expression marks, blemishes. and skin dryness. Masterful products are strong allies in these types of treatments, as they allow prescribers to associate actives that act in all manifestations of aged skin, promoting its rejuvenation, through firming, whitening, hydrating, antioxidants, among others. Objectives: this study aimed to outline the profile of the magisterial formulations that were dispensed for the treatment/prevention of skin aging. Methods: a descriptive, cross-sectional, qualitative study was carried out, based on the collection of information from the General Book of Dispensed Formulations from March 2021 to May 2021 of a compounding pharmacy in Vitória-ES. Results: the research found that 16.4% of the formulations for topical use are for skin aging, with 64.6% of these formulations prescribed by a dermatologist, in which the audience is predominantly women. The most frequent actives were hyaluronic acid, cerasomosides and Hyaxel® and the most used pharmaceutical forms were cream (27.3%) and gel (21.8%). In the requirement, associations between assets, 23.85% showed incompatibilities. Conclusion: given the results obtained, it is necessary to constantly act and train the pharmacist in order to avoid possible errors in the formulations, which may impair the effectiveness or the health of the patient.

Technological development of energy drink of natural origin: a technological prospection

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The energy drink market is in constant innovation. Each year, manufacturers seek new solutions to overcome the expectations of consumers who want new flavors, colors and above all more natural products that add some benefit to health and well-being. In this context, the technological and innovative development of an energy drink of natural origin becomes relevant, which will bring to the consumer market, several benefits, nutritional and functional quality, since it must contain a lower level of artificial additives and high levels of vitamins and antioxidants. For the method, a search and analysis of patents was performed through databases of the Instituto Nacional da Propriedade Industrial [National Institute of Industrial Property] (INPI), European Patent Convention (EPO), Databases of Latin America and Spain (LATIPAT) and World Intellectual Property Organizations (WIPO) using the term "energy drink" contained in the title or abstract, considering publications between 2015 and 2022 as selection criteria. In addition, only beverages related to Human Needs (Section A), and Food or Food Products (A23), subclass A23L were included in the search. And excluded duplicate patents and those with neither natural energy drink innovation nor energy drink development as a claim. A total of 277 filed patents were identified, of these, only 26 met the selection criteria. The results indicated that the elaboration of natural energy drinks is still characterized as a scarce branch that should be explored, given the benefits generated. Besides the fact that they promote energy when consumed, the analyzed patents of energy drinks made from plants or natural products showed numerous benefits such as antioxidant activity and antidiabetic, antidepressant, anti-aging due to the increased content of physiologically active components such as flavonoids and phenolic compounds.

Development of solvent-free eyebrow hair growth-promoting formulation

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Background: Topical formulations of minoxidil (MXS) are known for the treatment of alopecia. Traditionally MXS formulations are hydroalcoholic solutions, with adverse effects such as allergies, skin irritability and dryness. There is an increasing interest in innovative products specialized in the treatment of eyebrows hair loss with lower adverse effects and reduced dripping. Objective: Development of an optimized solvent-free formulation for MXS delivery to eyebrows with reduced dripping. Methodology: Poloxamer 407 (PLX) and hydroxypropylmethylcellulose (HPMC) were combined at three different concentrations formulations (15, 16 and 17% for PLX and 0.4, 0.8 and 1.2% for HPMC) together with MXS. The characterization was evaluated by the following tests: sol/gel transition point, viscosity at 25°C, drainage distance in porcine ear skin and drop weight. Through these data, an optimized formula (OF) and a comparison formulation (CF) were selected by surface response analysis (SRA). The drug release was evaluated by the static release profile and static skin permeation in Franz diffusion cells for 12 hours. Vertical permeation in modified Saarbruecken cells evaluated total skin (divided into three areas: upper, middle (gel application area), and lower) permeation for 12 hours. Results: The HPMC added to PLX improved the formulation characteristics, by SRA an OF was selected (PLX 16% and HPMC 0.4%). The OF release profile showed a controlled release of MXS in the first hour in relation to the CF (PLX 4% and HPMC 0.7%) and with no difference between the skin layers in the static permeation between the formulas (p<0.05). However, in the vertical permeation, the OF demonstrated localized MXS delivery at the contact point, showing a difference between the middle area and the other two areas (p<0.05) resulting from the radial permeation, while the CF flowed and permeated beyond the area of interest with high quantity in the lower area. Conclusion: Optimized formulation showed excellent efficiency in delivering MXS to the site of interest (middle third). Therefore, the obtained formulation increased its fixation when in contact with the skin, allowing for an easier, safer, and drip-free treatment.

Photoprotective Nanoemulsion Containing Linseed Oil (Linum usitatissimum L.) and Avobenzone and Tris-Biphenyl Triazine (nano) as Ultraviolet Filters

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Background: Skin damage caused by solar radiation, such as skin cancer, can be reduced by the use of sunscreens. Accordingly, natural products, e.g., linseed oil, have been used on the development of new sunscreens to increase formulations' photoprotective effect and provide them with additional characteristics, as antioxidant potential. Among different formulations, nanoemulsions are promising systems for this application. Objectives: The aim of this study was to develop a photoprotective linseed oil-based nanoemulsion with avobenzone and tris-biphenyl triazine (nano) (TBPT) as UV filters, which in association provide a broad spectrum of UV protection. Methods: The nanoemulsion was produced using the pseudo-thernary diagram approach, and avobenzone and TBPT was incorporated to the system. The nanoemulsion was evaluated by visual inspection, droplet size, polidispersity index (PdI), and zeta potential over the course of 60 days. In addition, the chemical stability of the UV filters and in vitro solar protection factor (SPF) was determined by spectrophotometric method. Results: The developed nanoemulsion was obtained using 9.9 % of linseed oil, 10 % of surfactants, 0.1 % of avobenzone, 8 % of TBPT and 72 % of water. The physicochemical characterization of the nanoemulsion revealed average droplet size of 132.5 ± 8.3 nm, PdI of 0.23 ± 0.03, zeta potential of -23.99 ± 1.28 mV, pH value of 6.77 ± 0.08, electrical conductivity of 1001.33 ± 3.06 µS/cm and SPF of 21. Further, the total content of UV filters remained stable over time, suggesting a preliminary SPF stability. Conclusion: The results of this study showed that the linseed oil-based nanoemulsion was kinetically stable and that the oil increased the photoprotective effect of the UV filters mixture, presenting itself as a promising candidate in the sunscreen development field.

Keywords: Nanoemulsion; Linseed oil; Avobenzone; Tris-biphenyl triazine (nano); Photoprotection.

Production of yogurt added of the pulp and peel of red jambo (Syzygium malaccense)

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Background: The red jambo (Syzygium malaccense) is a fleshy fruit, with a very reddish skin and with functional potential because it is rich in dietary fiber and antioxidant compounds such as ascorbic acid and anthocyanins. Considering that red jambo is not a well-known fruit, the production of food added of red jambo may be an important alternative to improve the use of this fruit, which is mainly found in the north and northeast regions of Brazil. Objectives: The present study aimed to produce a yogurt added of pulp and peel of red jambo. Methods: The fresh fruit was analyzed with regard to the proximate composition and for the presence of phenolic compounds. Next, the yogurt was produced using commercial starter cultures and added of pulp and peel of red jambo. Finally, the theoretical proximate composition of the yogurt was obtained by analysis of the ingredients in a database. Results: The results showed that the fruit has a high moisture content (84.24%), a substantial amount of dietary fiber (3.36%) and the presence of minerals (0.35%), proteins (0.67%) and lipids (0.45%). In addition, the fruit (peel and pulp) presented a remarkable amount of phenolic compounds (1 mg of Gallic Acid Equivalents per 100 g), which indicates the potential of this fruit for the production of functional foods. On the other hand, the yogurt presented a higher content of dietary fiber when compared to other yogurts available in the market, in addition of a natural pink color due to the peel of red jambo. Conclusions: We produced a yogurt with good nutritional value, with a natural pink color and a slightly acidic and sweet flavor. Such product may stimulate the consumption of red jambo and serve as an alternative source of bioactive compounds for the population of the north and northeast regions of Brazil.

Tyrosinase activity inhibition by ethanolic extract of Morus nigra leaves before and after chlorophyll removal

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Background: Tyrosinase is the main enzyme responsible for the enzimatic browning of foods and melanogenesis in mammals (1), which in many cases is an undiserable reaction. Research, identification and characterisation of potent tyrosinase inhibitors qualified for application in cosmetics is constantly increasing. One approach to prevent melanin-related disorders is based on the administration of bioactive plant compounds, as an effort to maintain skin evenness (2,3). Thereby, the ethanolic extract obtained from *Morus nigra* leaves was evaluated against the activity of tyrosinase in this study. Objective: This work aims to compare the inhibition of tyrosinase by the ethanolic extract obtained from *Morus nigra* leaves before and after chlorophyll removal. Methods: The leaves were collected in Brasília, Federal District. The plant material was dried, powdered and the extract was obtained by ethanolic percolation followed by filtration and concentration by rotatory evaporation. Finally, six lots of extract were generated. Then, half of each lot was subjected to chlorophyll removal by precipitation using methanol/water solution. Tyrosinase inhibition assay was performed for both halves of each lot and kojic acid was used as positive control. The analyses were performed in triplicate and the statistical analyses were accomplished using the software GraphPad Prism V6.0. Results: The overall IC50 of the tyrosinase inhibition evaluated ranged from 2,5433 ± 0,2939 µg/mL to 7,0296 ± 0,3255 µg/mL for the raw extracts and from 3,4696 ± 0,8021 µg/mL to 7,5323 ± 3,9288 µg/mL for the clear extracts. The IC50 value for the Kojic acid was 1,7466 ± 0,1862 µg/mL. Conclusions: The results obtained for the *Morus nigra* L. extracts in the assays demonstrated satisfactory values even at low concentrations. The raw extract had stronger tyrosinase inhibition in comparison to the clear extract. Yet, both extracts had close results compared to the positive control. Acknowledgments: FAP-DF, CNPq and CAPES for financial support.

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Production of bacterial cellulose as a natural active release system for the treatment of acne

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Acne is a highly prevalent skin disease and it is estimated that 9.4% of the world's population is affected at some point. However, because of the pandemic caused by SARS-CoV-2 (COVID-19), the prolonged use of face masks has caused a significant increase in the appearance of acne, which has also exacerbated the problem for people already affected by acne disease. This project aims to produce an active release system through a bacterial cellulose (BC) membrane incorporated with the natural actives Nisin and Mandelic acid, which are presented as an alternative solution with potential treatment effect against acne without expected side effects on the consumer and the environment. The production of bacterial cellulose was carried out from the growth of the bacterium G. xilynus in selective culture medium. The incorporation of the actives was performed according to the methodology developed by the research group. For the biological analyses, antimicrobial activity assays were performed with the membranes isolated and incorporated with the actives. The analyses performed were diffusion disc analysis and minimum inhibitory concentration (MIC) analysis. For the physicochemical analyses, Scanning Electron Microscopy (SEM) and Fourier Transform Infrared (FTIR) assays were performed. Through the biological tests performed, it was possible to observe that the pure bacterial cellulose does not present antimicrobial activity, but presents bacterial inhibition when incorporated with the actives under study. Through SEM analysis it was possible to perform the physicochemical characterization to evaluate the surface of the bacterial cellulose membranes. While in the FTIR assay it was possible to detect and characterize chemical groups in order to identify and evaluate the levels of oxidation, degradation, and the mixture of materials contained in the samples. With this study it is expected to develop an innovative product that uses natural alternatives, aiming to satisfy the concept of cosmetics free of environmental contaminants that present natural potential in the treatment of acne disease.

THEMATIC AREA:

Nanotechnology

Association of paclitaxel and an organoselenium compound in polymeric nanoparticles to overcome resistance of mdr cells

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Background: New approaches to increase the efficiency and selectivity of chemotherapeutic treatments require the incorporation of strategies that involve improving the performance of existing antitumor drugs, as well as their association with new potential compounds to overcome problems related to multidrug-resistant (MDR) cells. Objectives: To develop nanoparticles (NPs) containing an organoselenium compound in association with paclitaxel, and NPs with each compound singly, to verify possible synergism in MDR cells. Likewise, to characterize the NPs and to verify their hemocompatibility using erythrocytes isolated from human blood. Methods: Nanospheres were prepared by the nanoprecipitation method, using the polymer poly-ε-caprolactone and the surfactants Pluronic® F-127 and Span 80®, and then were evaluated for particle size, polydispersity index (PDI) and zeta potential. The MDR cell line used was NCI/ADR-RES (human ovarian cancer cells) and the cell viability was detected by the MTT assay. Compatibility with human blood was measured by quantifying hemoglobin release caused by membrane damage when in contact with the NPs. Results: The NPs presented nanometric size, PDI less than 0.2, which indicates homogeneity in the size distribution, and negative zeta potential. It was observed a synergistic effect of the organocalcogenium compound when associated with paclitaxel, evidencing a greater antitumor activity compared to the formulations with each compound separately. Moreover, the NPs proved to be non-hemolytic, with hemolysis rates lower than 2%. Conclusions: In this study, the proposed NPs were successfully prepared, with adequate physicochemical parameters. In addition, the results found after coencapsulation of the organoselenium compound and paclitaxel demonstrated synergistic antitumor action in the proposed cell line, and satisfactory hemocompatibility for all formulations. Finally, the coencapsulated nanocarrier system can be considered an important approach for overcoming obstacles in the antitumor treatment, especially the MDR effect.

Nanoemulsion containing kojic dipalmitate and rose hip oil: characterization, efficacy and cytotoxicity

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Background: Kojic dipalmitate (KDP), a highly lipophilic molecule, is employed to treat skin hyperpigmentation disorders such as melasma. Melasma treatments can be aggressive and challenging. Rose hip oil presents antioxidant and skin regenerating properties. Objectives: To associate KDP with rosehip oil, obtaining nanoemulsions, in order to facilitate the incorporation of the actives into aqueous vehicles and develop formulations with high performance aiming at melasma treatment. Methods: A high energy method (Ultra-Turrax®) was employed to develop nanoemulsions containing KDP (1 or 2 mg/mL), rosehip oil (5%) and surfactants (7.5%). Formulations were characterized regarding droplet size, size distribution, pH, morphology, KDP content, KDP incorporation efficiency and stability. Antioxidant and tyrosinase inhibitory activities were evaluated in vitro. Cell viability studies were performed in 3T3 cells. Scaling up was assessed increasing 10 times the volume of the initial batches. Results: The nanoemulsions presented KDP content and incorporation efficiency close to 100%, high antioxidant activity (over 70%) and depigmenting activity similar to ascorbic acid 1 mM, used as positive control. They presented droplet size of < 130 nm, suitable size distribution, pH of around 6, spherical morphology, zeta potential of around -10 mV and 30 days of stability under refrigeration. No cytotoxicity was observed for 3T3 cells in concentrations ranging from 0.06% to 1% of the formulations. The results showed no significant difference ($p \leq 0.05$) when comparing 1 mg/mL and 2 mg/mL nanoemulsions regarding the activities tested. It was possible to scale the 1mg/mL formulation up maintaining its characteristics. Conclusions: The nanoemulsions showed potential to be used in cosmetic formulations to treat melasma. The 1 mg/mL nanoemulsion appears to be the most suitable formulation. Acknowledgements: JCZ scholarship from CNPq, Brazil. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) Finance Code 001.

Transferrin-conjugated nanoparticles containing a new organoselenium compound inhibited tumor cells migration and overcame resistance of mdr spheroids

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Background: Overcoming multi-drug resistance (MDR) has been one of the most challenging problems of antitumor therapy. Therefore, the development of novel approaches to improve cancer treatment is fundamental. In this sense, the use of nano delivery systems has presented great results, especially by the conjugation of specific ligands (active targeting), such as transferrin (Tf). Objectives: To obtain nanoparticles (NPs) carrying the new organoselenium compound 5'-Se-(phenyl)-3-(amino)-thymidine (ACAT-Se), and conjugate Tf to the NPs. Moreover, to evaluate the NPs ability to inhibit cell migration, and their cytotoxic activity against a 3D tumor spheroid model. Methods: ACAT-Se PLGA NPs (ACAT-Se-NP) was obtained by the nanoprecipitation method, followed by Tf conjugation in the NPs surface using the EDC activation method (Tf-ACAT-Se-NP). The wound healing assay was used to evaluate the in vitro inhibitory effect of NPs on the migration of HeLa (human cervical cancer) and NCI/ADR-RES (MDR human ovarian cancer) cells. The NCI/ADR-RES spheroids were obtained using the hanging drop method, the spheroids were treated with the NPs for 12 days, and their size was measured and compared to the control spheroids (not treated). Results: The wound healing assay evidenced a greater inhibition of HeLa cells migration after treatment with ACAT-Se-NP in comparison to free ACAT-Se. Moreover, the complexation of Tf in the NPs improved even more the inhibition of migration, being also effective in suppress the migration of MDR cells (NCI/ADR-RES). The advantages of targeting Tf in NPs was also evidenced in the 3D spheroid model, being Tf-ACAT-Se-NP the most cytotoxic treatment in NCI/ADR-RES spheroids. Conclusions: Our results suggest that the Tf-conjugated NPs were able to suppress migration of HeLa and NCI/ADR-RES cells. Moreover, the Tf-ACAT-Se-NP effectively sensitized the MDR tumor spheroids. Therefore, the proposed NPs are a promising approach to actively and effectively improve the antitumor treatment, especially against MDR cells.

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Nanofiber-coated intravitreal device for age-related macular degeneration treatment

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Background: Age-related macular degeneration (AMD) is the major cause of visual loss in developed countries. It affects about 10% of the adults over 60 years. Its current treatment consists of monthly intravitreal injections of anti-VEGF agents that might be combined with corticosteroids. Intravitreal administration has limited therapeutic success due to the quick elimination of substances, requiring frequent injections that bring complications to the patient and low adherence to treatment. Sustained delivery devices are capable of releasing drugs locally, maintaining their therapeutic levels for prolonged periods, thus reducing systemic effects. Objectives: The present work proposes the development of intravitreal implants containing dexamethasone (DXM) coated with polymeric nanofibers containing bevacizumab (BVZ) to treat AMD. Methods: Poly lactic-co-glycolic acid intravitreal implants containing DXM were prepared by hot molding technique. Afterward, implants were coated with polyvinyl alcohol nanofibers loaded with BVZ. Those nanofibers were synthesized by electrospinning. Then, implants were characterized by scanning electron microscopy (SEM). Antiangiogenic activity and toxicity were also evaluated in chorioallantoic membrane assay (CAM). Results: Biodegradable intravitreal implants containing DXM coated with nanofibers containing BVZ were successfully developed. The efficiency of the coating process was visualized by SEM. The degradation test shows that nanofiber resists on the implant surface for at least 7 days. The CAM showed no toxic effects and confirmed the antiangiogenic activity. Conclusion: Biodegradable intravitreal implants containing DXM coated with polymeric nanofibers containing BVZ as a therapeutic strategy for AMD with decreased risks related to repeated intravitreal injections were successfully developed. This delivery system, combining two drug classes, is a promising alternative to the AMD treatment. Acknowledgement: FAPEMIG (Brazil) and INCT-NANOFARMA (FAPESP and CNPq/MCT, Brazil) for financial support.

In vivo evaluation of β-sitosterol nanocapsules in association with low-level laser on hair growth

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Background: Androgenetic alopecia (AAG) is a common disease, affecting men and women, and is the leading cause of hair loss. Its main causes are genetics and androgen-mediated follicular miniaturization. The disease develops from adolescence, when hormonal stimulation appears, and the most frequent symptom is thinning hair, in addition to increased sebaceous production and inflammation. The search for alternative treatments for alopecia leads to the use of products of natural origin, among them, β-sitosterol (BS), which has important therapeutic properties, such as antioxidant, antimicrobial, angiogenic, anti-inflammatory and modulator of the 5-alpha reductase enzyme. Still, non-drug resources are also employed, such as the low-level laser (LLL). Objectives: To evaluate the effect of polymeric nanoparticles containing BS associated or not with laser therapy on hair growth in an in vivo AAG model. Methods: BS-loaded nanocapsules (BS-NC) were prepared by interfacial deposition of preformed polymer method. The in vivo experiment was conducted (protocol number CEUA 5005090818) using Wistar albino rats (2-3 months old), and alopecia was induced by a daily injection of testosterone, for 21 days (0.5 mg/Kg/day). In parallel, the animals were treated topically with the BS-NC, BS-NC with LLL (660 + 830 nm) or finasteride (1%). After 21 days, all animals were euthanized, and the histological analysis of skin fragments was performed. Results: During the experiment, noticeable hair loss was observed after 12 days of subcutaneous testosterone injection, but no areas of alopecia were detected by the end of the experiment. In addition, photomicrographs of the skin showed a greater number of follicles in the groups treated with the combination of BS-NC and LLL. Conclusions: In the animal model of alopecia employed in this study, the combination of BS-NC with LLL showed similar efficacy to finasteride in stimulating hair follicle activity.

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Development of nanostructured lipid carriers loading ibrutinib for topical treatment of melanomas

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Introduction: Melanoma is the leading cause of death associated with skin diseases. Recently, tyrosine kinase inhibitors were introduced in therapy, and the obtained results have been promising. In this line, ibrutinib (IBR) has been highlighted and successfully explored to treat hematological and solid cancers. However, reports on the use of IBR for the treatment of melanoma are scarce and its low oral bioavailability is responsible for cases of undesirable adverse events. Objective: This work aimed at developing a topical formulation based on nanostructured lipid carriers (NCLs) for IBR incorporation as a proposal for the localized treatment of cutaneous tumors, with a focus on melanoma. Methodology: NLCs were obtained from a mixture of stearic acid (SA), pomegranate oil (PO), soy lecithin (SL), and Tween 80 (TW), which formed a microemulsion homogenized in ultraturrax and ultrasound. The proportion of each excipient and the homogenization time were chosen based on the experimental design, considering the size and polydispersity index (PDI) of the obtained nanoparticles. Compatibility between drug and excipients was determined by differential scanning calorimetry (DSC) and thermogravimetry (TG). Drug release in physiological media from the NLCs was assessed in Franz-type diffusion cells, mounted with cellulose acetate membrane. Results: The chosen excipients and methodology formed particles with sizes ranging from 176.3 to 1305.7 nm and PDI from 0.158 to 0.851. The NLCs obtained with 500 mg of SE, 500 mg of PO, 500 mg of SL, and 50 mg of TW sized 176.26 ± 29.21 nm (PDI = 0.182). The IBR thermal analysis showed two thermal events between 144.56 ºC and 154.52 ºC, and degradation from 333.91 ºC. The excipients reduced the IBR thermal events to 120.67 ºC and 143.83 ºC, and degradation to 182.01 ºC, but not compromised its stability, demonstrating compatibility. The CLNs controlled IBR release twice (p<0.05, T-test) compared to the control, which should concentrate its penetration in the skin layers when under topical application, avoiding a significant systemic exposure to the drug. Conclusion: Thus, the formulation developed seems promising for a topical treatment of melanomas with IBR.

Simulation of ferulic acid nanoemulsions and its experimental reproduction

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Background: Ferulic acid (FA) is a phenolic compound that has antioxidant, anti-inflammatory, anticancer and cytoprotective properties. However, it has limited bioavailability, low water solubility and is easily oxidized, all this makes its therapeutic application unfeasible. Thus, nanocarriers can be designed to mitigate undesirable effects, improve the stability and biological performance of this bioactive. Besides, computer simulation studies have played an important role in the development of new nanoparticulate systems through predictive mechanisms of molecular interactions. Classical molecular dynamics (CMD), which is widely used to study interfaces, in particular water-oil interfaces. Objectives: This study aimed to develop a FA nanoemulsion containing medium chain triglycerides (NE-FA) with a previous study of the interfacial tension by simulation of CMD, to optimize and improve stability of FA. Methods: The NE-FA was prepared (n=3), by spontaneous emulsification method and four concentrations of the FA were used: 0.5, 1.0, 1.5 and 2.0 mg/mL. After, the NE-FA were characterized by measuring their droplets size, zeta potential, pH, FA content and encapsulation efficiency. Besides, the stability of the NE-FA (25 ± 2) and the effect against UVC light were evaluated. Results: All NE had adequate characterization results and reproduced the expected behavior according to the CMD, then the size was between 100-200 nm, polydispersity index was lower than 0.2, content above 99% and encapsulation efficiency of 75%. NE-FA 1.5 mg/mL exhibited the best results in characterization and stability, keeping the content close to 95% for 60 days, also showed photoprotection effect on FA and demonstrated second-order photodegradation kinetic behavior. Conclusions: Thus, the CMD simulation proved to be a very powerful tool for understanding the process of developing nanocarriers at a level that is still largely unexplored and NE-FA 1.5 mg/mL has shown promising results to later be incorporated into topical dosage forms for better clinical use.

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Effect of co-delivered curcumin and melatonin into hyaluronic acid-coated nanoemulsions on 2D and 3D oral cancer cell models

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Oral potentially malignant disorders (OPMDs) are epithelial lesions or disorders with an increased risk for malignant transformation in oral cancer (OC). Curcumin (CUR) and melatonin (MEL) are chemopreventive drugs with significant clinical responses in OPMDs management. Due to the easy access to the oral cavity, the treatment of oral lesions may be achieved by using local drug delivery systems, such as mucoadhesive nanoemulsions (NEs). Hyaluronic acid (HA) is a mucoadhesive polymer that may bind to the CD44 receptor overexpressed in oral cancer cells and epithelial dysplasia. Objectives: To evaluate the cytotoxic effect of HA-coated NE co-delivering CUR/MEL (HA-NECUR/MEL) on OC (SCC9 and CAL27) and human non-tumorigenic keratinocyte (HACAT) cell lines using 2D and 3D models. Methodology: NECUR/MEL was prepared by spontaneous emulsification and electrostatically coated with HA. The cytotoxic effect in 2D cell culture was evaluated by the SRB assay. The 3D model (multicellular spheroid) was obtained by cell platting in non-adherent agarose. Then, after 24, 48, and 72 h of treatment, pictures from the spheroids were taken and measured using IMAGE J software. Results: The NEs showed nanometric size with CUR and MEL content of 85 µg/mL and 490 µg/mL, respectively. HA-NECUR/MEL exhibited a higher cytotoxic effect on HACAT, CAL27, and SCC9 cells than free drugs even when lower doses were tested (0.03 µM of CUR and 0.3 µM of MEL). The treatment of the multicellular spheroids with HA-NECUR/MEL (CUR 3.5 µM and MEL 34.5 µM) for 72 h reduced the sphere integrity, increasing significantly the sphere area by ~70% and ~15% for SCC9 CAL27, respectively, without affect the HACAT spheroid. Conclusions: Aside from the higher cytotoxic effect, these results suggest that HA-NECUR/MEL may selectively modify cell–cell adhesion of OC cell lines, indicating a promising approach for the management of OPMDs. Acknowledgments: The authors are grateful to CAPES for the financial support.

GC-FID method for the quantitative determination of β-Ketoindole derivative in polymeric nanocapsules

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Introduction: Indole and chalcone are related to biological activities as antioxidant and anticholinesterase. The β-ketoindole derivative have low solubility in aqueous medium, which makes it interesting to use nanoencapsulation to increase solubility and consequently, increase the probability of this compound to cross the blood-brain-barrier. For new compounds and new formulations, developing and validating an appropriate analytical is a necessary step. Objectives: This study aims to develop and validate a rapid and effective chromatographic procedure for the determination of a β-ketoindole derivative in polymeric nanoparticles using gas chromatography (GC) with FID detector. Methods: β-ketoindole-loaded nanoparticles were prepared by nanoprecipitation. Briefly, 100 mg PCL were dissolved in 30 mL of acetone, while 10 mg 1-(4-fluorphenyl)-3-(1H-indol-3-yl)-3-(4-methoxyphenyl)propan-1-one were dispersed in 160 mg Captex® and 80 mg of Span 80 and then added to the organic phase. All GC analysis performed with a Varian CP-3900 gas chromatographer coupled toa flame ionization detector and a CP-8410 auto sampler. Validation was performed according to the Analytical Methods Validation Guidance RDC 166/2017 from ANVISA. Evaluated parameters included selectivity, linearity, matrix effect, precision, accuracy, robustness, limit of quantitation and limit of detection. Results: Encapsulation efficiency (EE%) was 98.54% for the β-ketoindole in the nanoparticles. For β-ketoindole structural confirmation: nuclear magnetic resonance of hydrogen and carbon, mass spectrum, ultraviolet-visible and infrared techniques were used. The following parameters were evaluated: selectivity and specify, linearity, precision, interval, matrix effect, detection limit, quantification limit, accuracy, and robustness and proved adequate for the quantitative determination of this compound. Conclusions: The ketoindole compounds used in this work are volatiles, hence the use of GC-FID is, not only recommended, but also proved to be rapid, effective, and applicable to β-ketoindole derivatives. The validated method provides sufficient evidence as a reliable CG/FID analytical tool for measuring these formulation components.

Naproxen-loaded Mesoporous Silica Nanoparticles: Inorganic Carriers for 3D Printed Medicines

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Mesoporous silica nanoparticles (MSN) have been explored as inorganic drug carriers due to their high surface area and pore volume, providing high drug loading and amorphization of poorly soluble drugs, such as naproxen (NPX). NPX is an anti-inflammatory drug with solubility limitations that can lower its absorption and cause stomach irritation. The goal of this study was to load NPX in MSN to improve its solubility and as a suitable dispersible material in hydrogels for 3D printing. MSN were synthetized by the addition of a silica precursor in an alkalinized medium containing a surfactant, which afterwards was removed by calcination. A NPX ethanolic solution was twice added in the MSN (incipient wetness method) to achieve a drug loading of 10.12% (MSN-NPX-1) after the first and 16.78% (MSN-NPX-2) after the second incorporation. Formulations were characterized regarding particle size distribution (laser diffraction), surface area and pore volume (nitrogen adsorption-desorption isotherms), drug content (HPLC) and in vitro drug release profile (dialysis bag method, pH 6.8 phosphate buffer medium). MSN-NPX presented a monomodal and nanometric particle size distribution with good homogeneity (D[4,3]: 260 nm and 264 nm; Span: 1.48 and 1.45 for MSN-NPX-1 and MSN-NPX-2, respectively) and drug content close to the calculated (9.9 ± 0.3% and 18.3 ± 0.2%). The drug loading was also confirmed by the lowering of the surface area and pore volume: 1099 $m^2.g^{-1}$ and 0.412 $cm^3.g^{-1}$ for MSN; 780 $m^2.g^{-1}$ and 0.306 $cm^3.g^{-1}$ for MSN-NPX-1; and 667 $m^2.g^{-1}$ and 0.276 $cm^3.g^{-1}$ for MSN-NPX-2, respectively. The NPX release from MSN reached 90 ± 1% from MSN-NPX-1 and 79 ± 1% from MSN-NPX-2 after 4h, showing that the release rate was slower for the formulation with the highest drug loading. In addition, MSN-NPX-1 had a similar drug release profile compared with the drug diffusion profile from a NPX ethanolic solution (90 ± 5% in 4h). In conclusion, MSN is a promising strategy to increase the apparent aqueous solubility of NPX and a encouraging carrier to incorporate poorly soluble drugs into hydrogels for 3D printed oral dosage forms.

Targeted nanoparticles for sustained release of temozolomide

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Background: Glioblastoma multiforme (GBM) is the most frequent and most aggressive Central Nervous System (CNS) cancer. Temozolomide (TMZ), the first-line drug for the treatment of GBM, has clinical efficacy, but treatment with this drug is associated with the development of resistance in more advanced stages of the disease, in addition to the fact that TMZ has physical-chemical limitations that hinder its use, such as short biological half-life (~2 hours) and non-selective biodistribution, which promotes adverse effects from systemic toxicity. To overcome these limitations and increase the drug bioavailability, a promising approach is the encapsulation of TMZ in nanostructured lipid carriers (NLC) functionalized with specific ligands of EGFR receptors, such as cetuximab (CTX), which are overexpressed in GBM tumor cells, with subsequent dispersion of the nanoparticles in mucoadhesive thermo-responsive hydrogels (MTRH) for intranasal administration, a pathway that may be advantageous due to the absence of first-pass metabolism, avoiding the passage through BBB and optimizing its action in the CNS via bulb-olfactory transport. Objective: the objective of this work is to evaluate the potential of NLC functionalized with CTX dispersed in MTRH for intranasal administration of TMZ in the treatment of GBM. Methods: CTX functionalized NLCs containing TMZ (CTX-NLC-TMZ) was fully characterized regarding their physical-chemical properties and the release kinectics was investigated in vitro. Results: The TMZ solution showed a fast release with maximum concentration achieved < 2 hours. The nanoformulations were capable to promote a sustained release profile for over 72 hours, which is diserable to obtain therapeutic concentrations of TMZ in the brain for an extended time, preventing higher TMZ systemic concentrations, which is closely related to non-target toxicity and adverse effects. Conclusions: using the proposed methods, it was possible to obtained CTX-modified NLCs containing TMZ, which exhibited sustained release over 72 hours.

Development and characterization of nanosystems containing a new antifungal thiazolhydrazone compound

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Background: The 2-[2-(cyclohexylmethylene)hydrazinyl)]-4-phenylthiazole (RN104) stands out for its relevant activity against Cryptococcus fungi genus and for the low toxicity. RN104 is highly lipophilic (log P= 5.84) with low aqueous solubility at physiological pH, which impacts negatively its oral bioavailability. To overcome these limitations, nanotechnology is a very promising strategy, by means of the development of nanoparticles as the self-emulsifying drug delivery system (SEDDS) and the nanostructured lipid carriers (NLC). Objectives: To develop and characterize SEDDS and NLC containing RN104. Methods: SEDDS were prepared by weighing all components in a penicillin flask and magnetically stirring in a hot water bath. RN104 was added into the SEDDS after 24 h of its preparation through gentle magnetic stirring at room temperature. Hot high-pressure homogenization added to sonication was used to prepare NLC. The nanosystems were characterized in terms of particle size, polydispersity index (PDI), encapsulation efficiency (EE %) and Zeta potential (ZP). Results and Discussions: Among the prepared SEDDS, 3 formulations obtained satisfactory results remaining isotropic after 24 h and the emulsification time occurred within a period of up to 60 s. All these formulations contained a mixture of oil, hydrophilic and lipophilic surfactants and co-solvent. The physicochemical parameters of the emulsions formed after dispersion of these SEDDS in ultrapure water, simulated gastric fluid with and without pepsin, and simulated intestinal fluid, with and without pancreatin were all satisfactory for oral administration (particle size < 200 nm; PDI < 0,3; negative ZP; EE ≥ 70 %). NLC containing oil, solid lipid, hydrophilic and lipophilic surfactants, co-solvent and water were prepared and two formulations presented adequate physicochemical parameters (particle size < 200 nm; PDI < 0.3) and high EE (>95%). Conclusions: SEDDS and NLC developed and characterized were suitable for the RN104 oral administration and demonstrated a promising alternative for consolidation of the employment of this compound as an antifungal therapy. Future directions: The perspective is submitting the best formulation of each nanosystem to a pharmacokinetic study in a murine model to assess the improvement in oral bioavailability of RN104.

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Evaluation of Nanoemulsion for local transdermal therapy of Fenretinide as Chemoprevention Strategy

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Background. Despite the high worldwide incidence, there are few pharmacological strategies for breast cancer prevention, and the existing approaches have several adverse effects and low acceptance. In this work, we proposed a nanoemulsion (NE) for topical application of the retinoid fenretinide on the breast skin for breast cancer chemoprevention. The monoterpene limonene was incorporated with the double role of penetration enhancer and cytotoxic enhancer. Objectives We evaluated the influence of the composition of the oil phase (tricaprilyn or isopropyl myristate) and terpene concentration (1-5% v/v) on the physicochemical properties, rheological behavior, stability, and skin penetration of fenretinide. Methods. The NE was produced using probe sonication under an ice bath and characterized by dynamic light scattering (ZetaSizer NanoZS). Skin penetration was assessed in Franz diffusion cells using reverse phase UV-HPLC to quantify the drug. The maximum amount of fenretinide that could be dissolved in the oil phase was 1% (w/w). Stability was evaluated by assessing changes on droplet size and zeta potential for 6 months. Results. Nanoemulsions displayed Newtonian behavior, and decreases in viscosity were observed as limonene concentration increased. The droplet diameter of NE containing tricaprylin as oil phase was 1.5 to 1.9 fold smaller than those containing isopropyl myristate, but all of them displayed diameter bellow then 200 nm, polydispersity index under 0.2. and anionic zeta potential (-10mV). However, only systems containing isopropyl myristate with limonene at 1 and 2.5% were stable for 6 months, without phase separation or droplet size increases over 2-fold. Independent of the concentration of limonene, the NE did not show signs of irritation in the HET-CAM experimental model (hemorrhage, lysis and coagulation). The penetration of fenretinide increased with time between 3 and 12 hours, and the use of 2.5% to limonene provided a 1.7 fold higher fenretinide penetration in the epidermis (without stratum corneum)+dermis. Conclusions. The NE containing isopropyl myristate and limonene at 2.5% presented a suitable stability profile for 6 months and enhanced the skin penetration of fenretinide without promoting irritation signs in the HET-CAM model.

Development and characterization of pH-sensitive liposomes for theranostics of breast cancer metastasis

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Background: Breast cancer is the most life-threatening type of cancer for women. The high mortality rate (685.000 deaths in 2020, according to WHO) is mostly related to metastasis. Paclitaxel (PTX) is an effective antitumor drug, but its toxicity and lipophilicity impair the development of adequate formulations. IR780 is a fluorescent dye that can be entrapped in liposomes for diagnostic purpose. When the target is breast cancer cells, pH-sensitive liposomes are an interesting approach. Their lipid structure destabilizes in acidic endosome environment, which intensifies drug release, contributing to a more precise treatment. Objectives: To develop and evaluate pH-sensitive liposomes entrapped with PTX and IR780 for future treatment of breast cancer metastasis. Methods: pH-sensitive liposomes (LpH) were composed with DOPE, CHEMS, SPC and 100 µg/mL of PTX. Traditional liposomes (LPC) were constituted by SPC and PTX (100 µg/mL). Both samples were made by film hydration technique, followed by probe sonication (LpH) or extrusion (LPC). IR780 (40 µg/mL) and DSPE-PEG2000 were added by post incubation into both formulations. Size, entrapment efficiency (EE%) and drug loading (DL) were measured. The amount of drug retained in the vesicles after a pH switch from blood conditions (pH 7.4) to endosome acidic environment (pH 5.0) was determined by HPLC (PTX) and UV-VIS spectrophotometry (IR780). Results: LPC and LpH mean diameters were 136 nm and 148 nm. EE% of PTX was 99% and EE% of IR780 was 93% for LPC, with a DL of 11 µg/mg (PTX) and 3 µg/mg (IR780). As for LpH, 81% of PTX and 94% of IR780 added were entrapped, leading to a DL of 10 µg/mg for PTX and 4 µg/mg for IR780. PTX leakage was about 26% for LpH vs 13% for LPC after 30 minutes at 37°C. The IR780 release was low, but higher in acid environment (2% vs 9%). Altogether, that indicates that LpH is pH responsive, releasing 2 times more drug than LPC (P<0,05). Conclusions: LpH offered advantage over LPC regarding drug release on low pH conditions. This implies that LpH could perform better in vivo, ultimately leading to a more specific and effective treatment of metastasis.

In vitro/in vivo development of a population pharmacokinetic model for free and nanoencapsulated meloxicam in wistar rats

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Background. The advance of nanotechnology has expanded a range of opportunities for improvements in pharmaceuticals. The application of modeling and simulation, through its different approaches, is an alternative that allows the identification of sources of variability that change the behavior of the system, as well as the pharmacokinetic characteristics, from specific software. Objetctives. The present work aimed to describe a populational pharmacokinetic model (PopPK) of free (F-MLX) and nanoencapsulated (NCM) Meloxicam (MLX) in male Wistar rats (n=8/group). Methods. Each animal received a single dose of 5mg/kg i.v,; plasma samples were collected during 48h, which were later quantified on HPLC-PDA. The PopPK approach was applied, using the MonolixSuite™ 2020R1 (Simulation Plus, USA), for the concentration-time profiles. The evaluation for selecting the best model was obtained from the analysis of the goodness of fit graphs, visual predictive analysis, Akaike information criterion, -2LL (log-likelihood) and relative standard deviation (RSE%). In vitro release was performed using the dialysis bag method (phosphate buffer, pH 7.4) to describe blood MLX release. Results. Thus, a release constant (kr) was calculated in the DDSolver software and inserted into the NCM model. A two-compartment model with linear elimination, combined error, and normal distribution best described F-MLX. The values obtained were fixed in the NCM modeling, with the value of kr previously calculated. The best-fit model was a three-compartment model with linear elimination, combined error1 and normal distribution. F-MLX and NCM had a similar Volume of Distribution (V1=0.028, V1NC=0.034; V2=0.027 and V2NC=0.04 mL, respectively). However, for NCM, a third compartment was inserted to better fit the prediction of the parameters, with a relatively small intercompartmental difference when compared to the Q/Qnc of the free/nanoencapsulated group (Q2NC=0.00048 L/h) and relatively small V3NC. large (0.3mL), when compared to the other compartments. Results. These results demonstrate that it was possible to describe the behavior of nanoencapsulated MLX using in vitro and in vivo data as input data for the model developed in this study.

Development of theranostic nanohybrid systems for local delivery of methotrexate and nanoparticles based on iron oxide in breast cancer treatment

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World Health Organization indicated that breast cancer (BC) was one of the leading causes of women's deaths worldwide in 2019 (2.5 % of the cases). Among BC subtypes, the triple-negative (TNBC) poses major clinical challenges due to its poor prognosis and lack of specific therapies. Local drug administration into mammary ducts has been explored as an alternative approach for cancer targeting and reduction of the systemic adverse effects. In this work, we propose the engineering of novel theranostic nanohybrid systems that enable simultaneous local treatment and diagnostic of TNBC. The aims were to develop ethosomal nanosystems (NSs) for the delivery of the drug methotrexate (MTX) and nanoparticles based on iron oxide (NIOs), and to evaluate their effect on the viability of MDA-MB-231 cells. The ethosomes (ETs) were synthesized via ethanol injection method followed by extrusion. The NSs were obtained by individual or co-encapsulation of MTX and NIOs into the ETs. Blank ETs were also produced for comparison. The hydrodynamic sizes and colloidal stabilities were evaluated by dynamic light scattering. The MTX and NIO encapsulation efficiencies (EE) were calculated based on UV-Vis and energy-dispersive X-ray spectroscopies, respectively. Lastly, MDA-MB-231 cells viability was evaluated by the MTT assay after treatment with increasing concentrations of the NSs. The obtained NSs with average size of 100 nm were stable up to 30 days. The MTX and NIOs EEs were 64.8 ± 2.2 % and 64.2 ± 14.6 %, respectively, when individually encapsulated. The co-encapsulation resulted in 32 % and 8 % reductions in MTX and NIO EEs, respectively. Blank ETs reduced MDA-MB-231 cells viability in a concentration-dependent manner, with an IC50 of 25.9 µL of NS dispersion/mL of culture medium. ETs loaded with MTX or NIOs reduced the IC50 by 3.1- and 4.0-fold, respectively. Moreover, the co-encapsulation of these components reduced the IC50 by 6.3-fold in relation to the blank ET, suggesting a more pronounced cytotoxic effect when MTX and NIOs were combined. Hence, this work results support the potential applicability of nanohybrid systems for local management of TNBC.

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Development and characterization of P-cymene and myrcene loaded nanoemulsions

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Background: Aedes (Stegomya) aegypti L. is an insect of great medical importance because it can transmit several arboviruses to humans including yellow fever, dengue, zika, and chikungunya. The main ways to prevent arbovirus transmission are the use of repellents that provide physical protection and insecticides that eliminate insect larvae directly in the breeding sites. Derivatives of medicinal plants have been used since time immemorial as insecticides and repellents, especially essential oils (EO). The main constituents of EO are terpenes, mainly monoterpenes and sesquiterpenes, substances of low molecular weight and high volatility. Among the terpenes with insecticidal and repellent action, myrcene and cymene stand out. However, they have low water solubility and low stability, characteristics that make their use unfeasible. In this way, nanotechnology emerges as a strategy to improve the solubilities of these substances in water, in addition to the protection and delivery of these active ingredients. Among the nanostructured systems, nanoemulsions stand out, dispersions of oily droplets stabilized by an emulsifying agent in water. These systems allow the delivery of active ingredients, improve absorption, promote controlled release and allow the suspension of lipophilic active ingredients in aqueous environments. Objectives: Given the above, the objective of this study was to develop and characterize nanoemulsions containing the terpenes cymene and myrcene with potential larvicidal against Ae aegypti L. Methods: The nanoemulsions were obtained by a low-energy method and the hydrophilic lyophilic balance of the terpenes was determined. The obtained formulations were characterized by dynamic light scattering (DLS), nanoparticle tracking analysis and transmission electron microscopy. Results: The EHLr of myrcene and cymene were 15 and 16. These formulations presented a visual aspect characteristic of nanoemulsion. Through the DLS it was observed that the formulations had particle size around 120 nm, polidispersity index around 0.3 and zeta potential around -25 mV. Through MET, droplets with sizes less than 200 nm were observed. Conclusion: From the results it was possible to obtain stable nanoemulsions containing the terpenes cymene and myrcene. In the next steps, TENs will be characterized for their in vitro release and their activity against Ae. aegypti larvae

Aggregation of copper-oxide nanoparticles leading to a biphasic dose-response relationship in microbial viability assay

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Background: Copper oxide nanoparticles (CuO-NP) stand as promising antimicrobial systems that can be useful for developing new medicines or therapeutic innovations. However, besides displaying particular mechanisms of action, these systems are also susceptible to thermodynamical and physical-chemical features, such as pH, concentration, and ionic strength, implying that accurate investigations addressing their dose-response relationships against target microorganisms are fundamental challenges for the obtention of meaningful in vitro assays. Objective: To investigate the influence of morphology and concentration of CuO-NP on microbial viability. Methodology: In vitro microbial viability assays employing the S. aureus bacteria as a model were performed with different doses of CuO-NP, synthesized in different shapes. Spectroscopy techniques (optical absorption and photoluminescence) were used to track the occurrence of concentration-dependent modifications of the colloidal system. Results: In vitro microbial viability assays displayed a biphasic dose-response resulting in two concentration-dependent regimes, each characterized by specific IC50 parameters. Such a biphasic pattern does not depend on the CuO-NP's shape, as the IC50 values were not significantly different among the tested samples. Because CuO-NP displays characteristic optical properties, it was possible to track the occurrence of concentration-dependent modifications in this colloidal system by employing optical spectroscopy techniques (optical absorption and photoluminescence). Initial spectroscopic signatures begin to change at concentrations above 60µg/mL, which correlates precisely with the formation of the second phase in the viability assay. This behavior leads to a novel understanding that a modification occurring in the colloidal system is the cause behind the biphasic pattern. Furthermore, a careful interpretation of the spectroscopic signals reveals that such a modification is associated with the concentration-drive CuO-NP aggregation. Conclusions: These findings demonstrate a case study where the biphasic dose-response does not depend on the mechanism of action but on the aggregation of the antimicrobial agent, bringing novel and relevant discussions to the literature.

Quality by Design (QbD) approach for the development of microemulsion containing Passiflora setacea oil

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Background: Microemulsions are nanoscaled systems, particularly sized between 10 and 100 nm, capable of carrying natural oils and improving their organoleptic characteristics. The fixed oil obtained from Passiflora setacea stands out among others due to its composition rich in unsaturated fatty acids of the omega family, endowed with therapeutic potential, such as wound healing. Objectives: this work aims to develop a Passiflora oil-based microemulsion using Quality by Design as a tool. Methods: Initially, the fixed oil from P. setacea seeds was extracted using the Soxhlet method and had its chemical composition characterized using Gas chromatography–mass spectrometry. Then, designs of experiments were used to identify the ideal composition of oil, surfactants, and ratio of surfactants in relation to hydrodynamic droplet diameter, polydispersity index and visual classification. Results: The exploratory linear planning models were not significant, indicating the possible presence of curvature. The Box-Behnken design was satisfactory in predicting the influence of factors and their interactions, the model had r2 of 0.99, 0.91 and 0.97, for hydrodynamic diameter, polydispersity index and visual classification, respectively. Through the response surface and the desirability profile, it was possible to develop an optimized system, followed by its improvement for the topical route. These systems retained their physicochemical stability for 60 days presenting average hydrodynamic diameter of 20.8 ± 1.0 nm and PDI of 0.13 ± 0.01. Conclusions: The work hereby presented physicochemical stable microemulsions obtained through quality by design approach, which shows great capability for further investigation of biocompatibility and biological properties.

Keywords: Emulsified system; natural oil; Passiflora; experimental design; topical formulation.

Development of nanostructured lipid carrier (NLC) as an encapsulation system of Piper cernuum leaves extract for topical apllication

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Background: Piper cernuum leaves extract has activity against dermatophyte fungi and is promising for topical use. However, plant matrices have a complex mixture of compounds, causing challenges for formulations. The low solubility of actives of plant origin influences the bioavailability, requiring specific transport methods to improve some characteristics and performance. Therefore, nanostructured lipid carriers (NLC) are colloidal systems that have the potential to encapsulate these hydrophobic plant matrices. Objectives: The aim is to develop P. cernnum leaves extract-loaded NLC for topical antifungal application. Methods: Compritol®888 ATO and beeswax were chosen as solid lipids and isopropyl myristate as liquid lipid. The surfactants used were Alkest®400 and Tween®80. The percentage of lipid was fixed at 5% using a 10% surfactant system and extract proportions of 0.1% and 1%. NLC was produced by the nanoemulsification method. Particle size, polydispersity index, zeta potential, and pH value were determined. The physical stability of the formulations was observed visually and by centrifugation. Results: There was no phase separation between the dispersions which demonstrates the high stability of the systems. The pH of the beeswax dispersions ranged from 4.52-4.83 and for those consisting of Compritol®888 ATO from 5.98-6.22. In the dispersions of Compritol®888 ATO, the addition of the extract at 0.1% had no significant difference in the size and polydispersity variables, however, the concentration of 1% of the extract doubled the size of the NLC (32.01-67.87 nm), zeta potential varied from -3.68 to -4.70. For the dispersions made with beeswax, the most concentrated formulation with 1% extract showed a decrease in size (42.32 nm) with a polydispersion index of 0.322. The zeta potential in these samples ranged from -0.976 to -1.42. Conclusions: This study showed that it was viable to encapsulate the extract of Pipper cernnum leaves using two solid lipids of different origins - glyceride and ceride - with promising characteristics for topical antifungal product development.

Oral curcumin-loaded microemulsion: A potential nanocarrier intended for the treatment of COVID-19

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Background: Curcumin (Curcuma longa) is a curcuminoid with antiviral and anti-inflammatory activity. These properties unveil its potential in COVID-19 treatment. However, this molecule presents drawbacks, such as low aqueous solubility, low gastrointestinal stability, and low oral bioavailability, that compromise its clinical use. Alternatively, microemulsions, thermodynamically stable systems (10-100 nm), can be used to circumvent these limitations. Aims: To develop a curcumin-loaded microemulsion (Curc-ME) with gastrointestinal stability and sustained release, intended to prospect oral use for COVID-19 treatment. Methods: Curc-ME was prepared based on a previously developed pseudo-ternary phase diagram. Briefly, 15 % of PEG 30 Castor oil/Span® 80 (8.8:1.2), 5 % of Miglyol® 812 N, curcumin (20mg/g of oil) and 80 % of purified water were weighed and homogenized for 10 minutes by ultrasound probe at 40% of amplitude, 750 W, and 20 kHz frequency. Its physicochemical properties, entrapment efficiency (EE) by UHPLC, storage (25°C) and gastrointestinal stability and curcumin release in simulated gastrointestinal fluids (SGIFs) were evaluated. Results: ME-Curc presented spherical droplets (mean hydrodynamic size of 21.81 ± 0.20 nm) polydispersity index below 0.1, EE of 98 ± 0.73%, conductivity of 160 ± 3 μS cm−1, low surface tension (40.37 ± 0.48 dynes/cm) and viscosity of 5.33 × 10−3 ± 0.01 Pa.s. Curc-ME remained stable over 90 days under storage and under SGIFs conditions and revealed a modified and complex kinetics release (Weibull model) of curcumin in the SGIFs. Conclusions: Curc-ME was successfully produced, showed stability and modified curcumin release in gastrointestinal simulated environment. As a perspective, we expect to test Curc-ME as candidate to be further explored as a therapeutic agent in COVID-19 treatment.

Keywords: Nanosystems, oral delivery, Coronavirus

Lipid-polymeric hybrid nanoparticles plga-cholesterol as alternative drug delivery system for benznidazole

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Background: Benznidazole (BNZ) is the only available drug for the treatment of Chagas disease, in Brazil. Its low aqueous solubility and limited bioavailability lead to serious efficacy limitations. Hybrid lipid-polymeric nanoparticles (HLPNP) are colloidal systems considered as interesting alternative as nanocarrier for lipophilic drugs, such as BNZ. Objectives: This study aims to develop stable BNZ-loaded HLPNP and evaluates the influence of cholesterol in the physicochemical properties and drug loading of nanoparticles. Methods: Blank NPHLP and drug loaded NPHLP were prepared using an adjusted nanoprecipitation method. The organic phase of acetone (OP) containing PLGA:cholesterol (0.5%) at three different polymer:lipid ratios were evaluated (90:10; 75:25; 50:50), sorbitan monoeleate (0.3 %), BNZ (500 µg/mL) were tested. 6 mL of OP was drippen (2 ml/min) into the 14 mL of aqueous phase (AP) contained poloxamer 407 (0.25%) at 25 °C, under constant stirring at 720 rpm and remained stirring overnight to solvent evaporation for 24 h. The systems were characterized in size and polydispersity index (PDI). Entrapment efficiency (EE) was performed by indirect method use UV spectroscopy. Results: Samples of blank HLPNP prepared with PLGA:cholesterol at a 90:10 ratio exhibited improved characteristics, the particle size was 141.3 ± 5.4 nm and PDI 0.05 ± 0.012. The cholesterol increment to 75:25 and 50:50 ratio induced particles with 164.4 ± 0.9 nm and 170.3 ± 6.9 nm, respectively. All formulations wiere considered suitable to BNZ loading, but the highest drug loading efficience (38%) was observed within PLGA:cholesterol of 90:10. The increment of cholesterol decreased drug loading and induces drug phase separation. Conclusions: The results demonstrate a promising and innovative nanoplatform. Further studies to increase BNZ entrapment are necessary, as well as performance studies and biological tests.

Rapanea ferruginea bark extract-loaded nanoemulgel: in vitro safety and photoprotection evaluation

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Background: *Rapanea ferruginea* is a Brazilian plant popularly used for the treatment of itching, rashes, hives, and eczema. The bark extract has shown anti-inflammatory and antinociceptive activities. Nanosystems, such as nanoemulsions and nanoemulgel, are dermatological carriers that improve drug release and dermal drug permeation. *R. ferruginea* extract-loaded nanoemulsions showed improved *in vitro* and *in vivo* anti-inflammatory capacity. Objective: To evaluate the safety and photoprotection effects of *R. ferruginea* bark extract-loaded nanoemulgel using *in vitro* models. Methods: Nanoemulsion was prepared by the phase inversion method. *R. ferruginea* bark extract-loaded nanoemulgel was prepared using nanoemulsion:carboxy vinyl gel proportion1:2. The antioxidant activity of the extract was evaluated by DPPH method. The extract and nanoemulsion cytotoxicity (1, 10, 100, and 300 µg/mL) on L929 cells were evaluated by MTT method. The irritative potential was tested on L929 cells through an agarose-overlay method. Photochemoprotective (UVA and UVB) effect was evaluated using L929 cells and irradiation method and quartz plates. A commercial sunscreen FPS 30 and the base nanoemulgel were utilized as controls. The photoprotection factor was calculated by accessing the viability of irradiated and non-irradiated cells. Results: The extract presents antioxidant activity in DPPH method with CE50 of 0.95 mg/mL ± 0.03. The extract and nanoemulgel did not exhibit cytotoxic effects in L929 cells. Pure *R. ferruginea* extract and loaded formulations did not present irritative potential. The extract (100 and 300 µg/mL) and the nanoemulsion show a photoprotective effect on both UVA and UVB radiations. *R. ferruginea* extract-loaded nanoemulgel show a photoprotection factor of 12.96 ± 2.29 and the base gel provided an insignificant photoprotection factor of 1.49 ± 0.50. Conclusion: The results show the antioxidant and photoprotective potential of the *R. ferruginea* bark extract and the respective loaded nanostructured system, which can be considered a promising active ingredient in the development of new products for skin care and photoprotection.

Polymeric nanogels-loaded with Eugenia uniflora dry extract for topical delivery

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Background: Antifungal activity of Eugenia uniflora L. dry extract has been demonstrated, mainly due to the principal markers (gallic acid – GA, ellagic acid – EA, and myricitrin – MYR). Therefore, developing a topical formulation containing Eugenia uniflora's extract can be promising in treating cutaneous mycoses. However, the penetration of substances into the skin is often challenging, so several penetration enhancer systems have been studied, including nanogels. Objectives: This study aimed to develop polymeric nanogels containing different concentrations of sorbitan monooleate (Span® 80) and evaluate the impact of this excipient on the performance of the topical formulations. Methods: The formulations were developed with 18% of the polymer, 3, 6, and 12% of span, and 4% (w/v) dry extract (DryExt) (PS3%-DryExt, PS6%-DryExt, and PS12%-DryExt). GA, EA, and MYR were quantified by a previously validated High-Performance Liquid Chromatography method. The formulations were characterized as to the mean diameter, PdI, zeta potential, and microstructure by transmission electron microscopy (TEM). The formulations' stability and rheological behavior, as well as the release and permeation of the markers, were evaluated. Results: The systems presented nanometric size (~ 200 a 400 nm) and were polydisperse (PdI from 0,2 to 0,5). The TEM showed spherical structures with dark and thick halos, indicating the possible formation of polymeric vesicles. All formulations were stable for 30 days. The increase of span concentration led to the increase of viscosity and reduction of the nanosystems' sol-gel transition temperature, indicating that span possibly participates in forming nanosystems forming mixed systems. In general, the increased span concentration promoted greater release and penetration of the actives into the stratum corneum. For instance, PS12%-DryExt increased the GA and MYR permeation by 5-fold, concerning PS3%-DryExt, in 24 h. Conclusion: The addition of increasing span concentrations made the formulations more viscous, which makes the formulations more suitable for topical application. The release was not significantly changed by the increase of viscosity, possibly due to forming mixed systems. The increase in active release and permeation indicates that these systems may be promising in treating cutaneous mycoses.

Raloxifene nanogels for transdermal drug delivery

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Background: Raloxifene hydrochloride (RLX) is a selective estrogen receptor modulator. Oral use shows a bioavailability near 2% due to extensive first-pass metabolism. Thus, the transdermal administration from RLX has been one of the strategies used to improve bioavailability and reduce the side effects. Objective: Obtaining nanogels for transdermal delivery of RLX. Methodology: Four polymers were selected for the development of the formulations, these being: polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol copolymer (P1), polyethyleneglycol 400 (P2), poly(ethylene oxide)-poly(propylene oxide) derivative copolymer (P3) and copovidone (P4). Accelerated stability studies demonstrated the binary combinations and the most promising proportions of polymers. After preparation, the formulations were characterized by average size, polydispersity index (PdI), zeta potential, pH, and drug content. In addition, characterization was performed after 15 and 30 days of storage at 4 °C. Rheology was performed, and the in vitro permeation in Franz diffusion cells was evaluated. Results: Six most promising formulations were obtained, three dispersions with P1:P2 and three with P3:P4, all in the proportions of 1:3, 1:1,5 and 1:1 (w/w). P1:P2 dispersions formed monodisperse micelles with sizes between 30 and 70 nm. P3:P4, on the other hand, resulted in polydisperse systems with nanometer structures ranging from 30 to 400 nm. 5 mg/mL of RLX were added to the formulations. All six formulations demonstrated physical and chemical stability, except P1:P2 (1:1,5), which showed a reduction in RLX content after 30 days of storage. The formulations P3:P4 showed a distinct rheological behavior when the temperature variation was used, not exhibiting the characteristic sol-gel transition of P3. The formulations P3:P4 increased approximately 12 times the permeation of RXL to the EC and the other layers (remaining skin) compared to the same formulations with P1:P2. Conclusion: Formulations with P3:P4 have shown to be promising for RLX transdermal delivery.

Anacardic acid loaded-zein nanoparticles: an innovative approach for caries prophylaxis

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Background: Anacardic acid is the major phytochemical found in the oleoresin obtained from cashew nut shells of Anacardium occidentale. This phytochemical has demonstrated remarkable antibacterial activity. Objective: This study aimed to prepare zein nanoparticles loaded-anacardic acid and evaluate the biopharmaceutical properties and antibacterial potential over Streptococcus mutans. Methods: Nanoparticles were prepared by controlled nanopreciptation of zein. The obtained formulations were characterized in terms of size, pdI and zeta potential and submitted to the conditions found in the oral environment in order to evaluate its stability. Atomic force microscopy was used to evaluate the substantivity of the nanoparticles in specimens of bovine enamel. The nanoparticles inhibitory (MIC) and bactericide (MBC) concentrations were determined, Finally, the formulations were tested against a 24h pre-formed Streptococcus mutans biofilm. Results: The nanoparticles were found to adhere to the enamel surface after 30 seconds soaking followed by abundant cleansing with demineralized water, while its substantivity was found to last over seven days after incubation in natural saliva. This nanoformulation was stable in the acidic pH (4.5) of the demineralization solution, while it dissolved in the remineralization solution (pH 7.0). The MIC and MBC of the nanoparticles were 0.36µg/ml. Moreover, its activity against the cariogenic S. mutans biofilm was equivalent to that of chlorhexidine gluconate 0.12%. Conclusions: Zein nanoparticles containing anacardic acid demonstrated good biopharmaceutical properties and could become an alternative for caries prophylaxis, promoting potent antibacterial effect together with a long-term enamel substantivity up to 7 days.

Development and characterization of a biomimetic nanoparticle coated with human Calu-3 lung epithelial cell membrane

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Background: Interest in developing biomimetic nanoparticles has grown since cell membrane-coated nanoparticles can replicate certain cellular functionalities. This platform is capable of offering target selectivity, immune evasion, and mimicking its parent cells. Objectives: To develop and characterize biomimetic nanoparticles coated with the human Calu-3 lung epithelial cell line membrane and investigate its applicability as a decoy to pathogens like the SARS-CoV-2 virus. Methods: To obtain cell membranes, human Calu-3 lung epithelial cells were cultured in T175 cm2 culture flasks to full confluency and detached with a cell scraper, and then suspended in a hypotonic lysing buffer. The membranes were separated by a differential centrifugation method. Poly (DL-lactic-co-glycolic acid) (PLGA) nanoparticles were prepared by a nanoprecipitation method to fabricate the polymeric cores. For coating polymeric cores, the Calu-3 cell membranes were mixed with PLGA nanoparticles and then sonicated in the bath sonicator, resulting in Calu-3 NP. The formulations were characterized by size and polydispersity index (PdI) using dynamic light scattering (DLS), zeta potential, and transmission electron microscopy (TEM). The membrane proteins were characterized by BCA assay and western blot. Results: Polymeric cores and Calu-3 NP exhibited average diameters of 100 and 140 nm respectively. Zeta potential of membrane-coated nanoparticles was lower “in module" than naked nanoparticles. TEM images showed the addition of a cell membrane bilayer to the polymeric cores. BCA assay demonstrated the presence of proteins in the biomimetic nanoparticle surface. Western blot revealed the biding capability of angiotensin-converting enzyme II (ACE2) present in Calu-3 NP. Conclusions: These results demonstrate that we have developed a functional biomimetic nanoparticle by coating a polymeric core with the cell membrane of a human lung epithelial cell, maintaining the biorecognition capability of cell membrane proteins.

Development of polymeric nanocapsules containing a new triazole derivative of eugenol with potential activity against Leishmania spp.

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Introduction: Visceral Leishmaniasis is a neglected parasitic disease and available treatments for human is based on parenteral formulations with important limitations and serious side effects. Different strategies have been used to develop new options, such as the use of drug nanocarriers and the synthesis of new active molecules. Triazole derivatives of eugenol have shown important anti-Leishmania activity in vitro. However, the low water solubility of these compounds may limit their use. The use of polymeric nanocarriers can circumvent these limitations, in addition to promoting a reduction in toxicity and a potential to increase biological activity. Objective: This work aims to develop and characterize polymeric nanocapsules (NC) to encapsulate a new triazole derivative of eugenol, that present an activity against Leishmania spp. in vitro. Methodology: NC prepared by the nanoprecipitation method were characterized in terms of average size, polydispersity index (PdI), zeta potential and encapsulation efficiency. The in vitro release kinetics was performed using the reverse dialysis method in two different release media (pH 4.5 and 7.4). Cytotoxicity toward host cells was determined in the RAW 264.7 macrophage cell line after 24h and 48h incubation with free and encapsulated active compound. Results: NC showed a mean size of150 nm with narrow size distribution (PdI = 0.114), negative zeta potential (-51 mV), and high efficiency of encapsulation (85%). After 48h, 47% of the encapsulated compound was released from the NC, without difference in the profiles following the different pHs. NCs reduced cell viability in a dose-dependent manner, presenting a CC50 of 18µM after 48h of incubation. Conclusion: The developed polymeric oily core-NC presented suitable characteristics for intravenous administration, controlled drug release, being promising for the development of new treatments for visceral leishmaniasis.

Nanoencapsulation improves radical scavenging property, photostability and promotes sustained in vitro release of Sesamol

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Background: The scientific literature highlights many health benefits provided by Sesamol (SES), for example, its antioxidant and antiinflammatory properties. Therefore, technological approaches should be applied to better explore SES therapeutic application. In this context, the development of nanocapsules has been recognized as a potential alternative to maximize the biological properties of drugs. Objectives: The study aimed the development of SES loaded nanocapsules suspensions and the evaluation of nanoencapsulation impact on antioxidant activity and release profile. Methods: SES nanocapsules suspensions (1mg/mL) were prepared by interfacial deposition of preformed polymer technique (n=3). The mean particle size and polydispersity index (PDI) were measured using dynamic light scattering (DLS). In addition, the granulometric distribution was determined by laser diffraction. The zeta potential was determined by electrophoretic mobility and the pH values were evaluated using a potentiometer. Encapsulation efficiency and sesamol content were determined by HPLC. The evaluation of SES release profile from the NC SES was performed using the dialysis bag diffusion method using phosphate buffer pH 7.4 at 37°C as release medium. Scavenging activity was assessed by the 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid-ABTS) and 1-1-diphenyl-2-picrylhydrazyl methods. The photostability assay was performed by exposure SES in free or nanoencapsulated form to ultraviolet lamp UVC. Results: The nanocapsules showed nanometric size (127 nm), low polydispersity index (< 0.2), pH value at acid range (5.06), high values of zeta potential (-20.4 mV), drug content of 100%, and encapsulation efficiency of 65%. The nanoencapsulation protected SES against UVC-induced degradation and increased the scavenging activity assessed by the ABTS and DPPH radicals. The results of in vitro release profile demonstrated that the nanocapsule suspensions presented an initial burst effect followed by a prolonged SES release. Conclusion: Therefore, our results suggest that nanoencapsulation could be a promising approach to SES therapeutic applications. Financial support: CAPES, FAPERGS.

Development and quality and safety evaluation of nanoformulation containing azelaic acid for the treatment of rosacea

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Introduction: Rosacea is a skin disease characterized by inflammation, where most affected individuals present Fitzpatrick I and II. The drug azelaic acid (AZA) can be used as a possible therapeutic option against this disease, but it has unfavorable properties that limit its clinical use. In this sense, the association of AZA to polymeric nanocapsules (NC) may represent a promising alternative since they have several advantages, among them reducing adverse effects of drugs. However, besides the technological development of this type of formulation, it is necessary, in parallel, to develop and validate an analytical methodology that can be used to assist in the steps of formulation characterization and quantification of AZA. It is also essential to evaluate the safety profile of this formulation so that its clinical use can be envisaged. Objective: To develop and characterize NC containing AZA and evaluate this innovative nanoformulation's safety profile. Methods: NC containing AZA (0.5mg/mL) (NC-AZA) or without AZA (NC) were obtained by the nanoprecipitation method. In addition, the safety profile of NC-AZA and NC was evaluated on fibroblast (primary human gum line) and keratinocyte (HaCaT) cell lines. The non-encapsulated drug was also used as a control (AZA). Results and Discussion: The analytical method was validated and found to be linear (R^2 0.999), accurate (relative standard deviation less than 5%), and specific for the quantification of AZA. The content analysis showed a recovery of AZA of 105.77%, and 42% of the encapsulated drug in NC. It was observed that NC-AZA and NC showed only a nanometric population of around 220 nm with a low polydispersity index (less than 0.2), negative zeta potential (around -13 mV), and pH close to skin pH. Also, NC-AZA and NC did not cause toxicity at a dose of 0.05mg/mL. Conclusion: Developing a nanoformulation containing AZA with all the quality parameters was possible. Future investigations are necessary to identify the differentials of the developed formulation.

In vitro cytotoxicity of theranostic polymeric nanocapsules decorated with ligand for active targeting to breast cancer cells

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Background: Advances in nanotechnology have enabled the development of nanotheranostics that combine selectivity, monitoring the biodistribution by imaging and reliable diagnosis of disease progression. The fluorescent photosensitive compound IR780 is a promising molecule for photodynamic therapy. IR780 has fluorescence emission in the wavelength range of 807-823 nm with a high quantum yield and able to generate cytotoxic reactive oxygen species after photoactivation. Due to the high lipophilicity of this photosensitizer, the use of polymeric nanocarriers has been proposed to facilitate administration. Objectives: In this work we developed polymeric nanocapsules (NC) containing the fluorescent marker IR780 covalently bound to polylactide (PLA) with or without carbohydrate derivative as a ligand at NC surface, and we evaluated cytotoxicity of them against 4T1 cells by the neutral red cell viability method. Results: The mean size of NC was 170 nm, zeta potential of -35 mV and polydispersity index lower than 0.3. NC derived from the biodegradable polymer PLA containing ligand covalently bound to the polymeric wall showed higher cytotoxic against murine breast tumor cells (4T1), with lower IC50 when compared to NC without ligand. Conclusion: The carbohydrate ligand covalently bond to the nanocarrier increases the cell internalization and cytotoxicity, paving the way to potential applications in breast cancer therapy. Acknowledgements: This work has been supported by the following Brazilian research agencies: CAPES, CNPq, FAPEMIG and PROPPi/UFOP.

Development, characterization, and safety evaluation of polymeric nanocapsules containing azelaic acid delivered in a semi-solid formulation

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Introduction: Rosacea is a dermatological skin disease characterized by chronic and progressive inflammation. Thus, azelaic acid (AZA) is used to treat rosacea. However, it has some adverse effects, such as increased skin irritability, itching, redness, and burning, leading to non-adherence to treatment. Gum tragacanth (TG) is a slightly acidic complex polysaccharide that has interesting adhesive properties without causing toxicity. In order to circumvent some limitations that AZA presents, nanotechnology can be used as a strategy to reduce adverse effects or improve the physicochemical characteristics of this drug. Incorporating polymeric nanocapsules containing AZA in TG becomes an interesting and innovative work since it is desirable to modulate the release of this drug in the skin to propose a new treatment for rosacea. Metodology: The semi-solid formulation was obtained through manual homogenization of NC-AZA directly into TG (2.5%) and named (TG/NC-AZA). In addition, hydrogels containing AZA in their non- encapsulated form (TG/AZA) and without the presence of the drug (TG) were prepared and used as controls in the evaluations. Furthermore, for the semi-solid formulations, the viscosity (Brookfield, USA), and the adhesion was evaluated in a texturometer (TA.XTplus Texture Analyzer; Stable Microsystem, Godalming, UK) using mucin and pig ear. The safety profile of the hydrogels was evaluated in embryonated eggs (HET-CAM) and compared with negative control (0.9% NaCl), and positive control (01M NaOH and 0.1% sodium lauryl sulfate). In addition, cell damage on CAM-TBS. Results: TG/NC and TG viscosity presented a pseudoplastic profile with the Herschel Bulkley model and a confidence index above 99%. The pH is TG/NC (5.00) TG (6.75) TG/NC-AZA (4.32), and TG/AZA (3.64). When evaluated, the adhesiveness profile in TG/NC mucin showed a higher work average when compared to TG (2062.61mN.mm ± 4.96; 1643.80mN.mm ± 7.38), and when evaluated in ear skin of porcine, there was no significant difference (46.405 mN.mm ± 5.75; 46.853 mN.mm ± 11.93), respectively. In the evaluation of the safety of HET-CAM, TG, TG-AZA, TG/NC, TG/NC-AZA and CAM_TBS showed a safe profile in the treated groups showing low irritation. Conclusion: The development of polymeric nanocapsules containing AZA delivered in TG represents a breakthrough in research involving its application in dermatology and cosmetics. It can potentially be used as a new treatment for rosacea disease.

Development, physicochemical and biological evaluation of alpha-tocopheryl succinate and doxorubicin-loaded liposomes

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Background: Doxorubicin (DOX) is the most effective drug used to treat breast cancer. Cardiotoxicity and low penetration in solid tumors limit its clinical use. Although the DOX encapsulated in liposomes allows the reduction of the adverse effects, it does not bring benefits in antitumor efficacy compared to the DOX solution. pH-sensitive liposome containing associations of antitumor agents may be a strategy to improve drug delivery at the cellular level and thus increase its antitumor efficacy. Objectives: Develop pH-sensitive liposomes containing alpha-tocopheryl succinate and doxorubicin (pHSL-TS-DOX) and evaluate their biological behavior in breast tumor experimental model compared with a formulation used in the clinic. Methods: The formulations were prepared by hydration of lipid film in the presence or not of ammonium sulfate and characterized by diameter, polydispersity index (IP), zeta potential, encapsulation efficacy and release profile. In vitro (cytotoxicity, cell uptake, cell cycle analysis and nuclear morphology) and in vivo (antitumor efficacy, DOX plasmatic concentration and toxicity) studies were also carried out. Results: Spherical vesicles of homogeneous content with an average diameter of less than 200 nm, monodisperse, with zeta potential close to neutrality, encapsulation content above 90% and stable for up to 30 days were obtained. The formulation showed a controlled release at pH 7.4 and a high release rate at pH 5.0, given its pH sensitivity. In in vitro studies, a higher rate of cellular uptake of DOX was observed from the developed formulation, which allowed more advanced levels of apoptosis and block of the cell cycle than the commercial formulation. pHSL-TS-DOX reached a lower plasma concentration of DOX in healthy animals; however, in animals bearing tumors, there was a high accumulation of DOX inside the tumors, which may justify its better performance in studies of antitumor activity. It conferred cardiac and liver protection and did not induce weight loss or myelosuppression. Conclusions: This formulation proved to be safe and a potential alternative for breast cancer treatment. Financial support: FAPEMIG, CNPq, CAPES.

Development of thiolated chitosan-capped silver nanoparticles: an approach to the detection of leishmaniasis

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Background: Leishmaniasis belongs to tropical neglected diseases. The early diagnosis helps to conduct the management of the disease, reducing the damage. Serological and immunological tests have been developed to facilitate the diagnosis, detecting proteins and surface antigens specific to the promastigote or amastigote forms. The use of properties from metal nanoparticles combined with biopolymers has been studied to reduce detection time. Chitosan has chemical groups that could be modified to improve its solubility, expanding its applications. Objectives: For this purpose, chitosan was modified to obtain thiolated chitosan (TCh) and subsequently was used to stabilize silver nanoparticles (TCh-AgNP), pursuing a particle that can improve the diagnosis of Leishmania. Methods: Chitosan modification was performed by coupling chitosan with 3-mercaptopropionic acid through the EDC-NHS mediated reaction. TCh was characterized by Ellman's assay to quantify SH groups. The TCh-AgNPs were produced by a chemical reducing method. Briefly, TCh was reduced by sodium borohydride followed by the addition of an aqueous solution of silver nitrate. The detection of the anti-leishmaniasis antibodies was performed by SPR (surface plasmon resonance) analysis. The anti-K39 monoclonal antibodies and the TCh-AgNPs anchored with the antibodies were deposited at different concentrations (10, 20, 30, 40, and 50 µg mL-1) on SPR apparatus and the laser reflection angle variation was observed over time. Results: The amount of thiol groups in the polymer was 2.16 mM, and 0.89 mM of these were founded in the free form (41%) and 1.27 mM in disulfide bonds (59%). The application of TCh as the stabilizing agent of AgNPs resulted in the redshift of the wavelength maximum of the scanning spectrum (387 nm for AgNPs and 420 nm for TCh-AgNPs), size increasing from 29.1 ± 2.5 (AgNPs) to 66.1± 1 nm (TCh-AgNPs), and the decrease of zeta potential from -36 mV (AgNPs) to -26 mV (TCh-AgNPs) indicated a surface coating of AgNPs by TCh. The time of K39 protein detection by the free antibody occurred close to 1h, whereas the antibody-anchored TCh-AgNP reduced the detection time to about 15 minutes. Conclusions: The stabilization of the TCh-AgNPs was successful and the anchoring of antibodies on its surface reduced the kinetics of K39 detection.

Nanoemulsions containing phytol as pharmacological alternative for the treatment of cutaneous leishmaniasis

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Introduction: Leishmaniasis is a neglected tropical disease caused by protozoa of the genus Leishmania spp., that mainly affects populations from poorer countries. The disease treatment is very limited, expensive, toxic to the patient, and the parasites present resistance to chemotherapy. Phytol, a chlorophyll component of the diterpene class, is found abundantly in nature and has extensive biological activities reported in the literature, including the antiparasitic. Nanoemulsions (NE) are colloidal dispersions of two immiscible liquids, usually, water and oil, that were stabilized by an emulsifying agent and presented a droplet size less than 500 nm. Objectives: To develop biocompatible NE containing phytol, the characterize the systems physiochemistry, such as size, Polydispersion Index (PdI), Zeta Potential (PZ), pH and macroscopic characteristics, were evaluated in order to achieve the NE that shows stability during 30 days. Methods: The NE were obtained through emulsification by phase inversion, at room temperature. Composition of the oily phase: 5% mixture of surfactants (polysorbate 80 and soya bean phosphatidylcholine), 5% of soybean oil, and 10% of glycerin; aqueous phase: 10% of polaxamer 407 dissolved in ultrapurified water. Phytol was added at a concentration of 10 mg/g. The physicochemical parametrons for NE formulations were measured for 30 days and any phase separation monitored. Results: The NE developed presented less turbid and liquid aspect, which remained over the 30 days, so macroscopically throughout the study there was no observed any phenomenon of instability. The white system throughout the 30-day stability study presented an average size of 142.1 ± 2.87 nm, PdI of 0.18 SD ± 0.03, PZ of -12.9 mV SD ± 4.18 and pH 6.02 SD ± 0.44. phytol loaded NE presented an average size of 189.9 nm SD ± 15.34, PdI 0.21 SD ± 0.04, PZ -15.4 mV SD ±3.31 and pH 6.04 SD ± 0.32, so in both systems during the whole study there were no statistically significant changes, being a promising suggestion of stability. Conclusions: All the testes NE formulations were considered stable and suitable for in vitro testing for cytotoxicity and antileishmanicide activity. The project was carried out with financial contribution from Capes/CNPq under n° (311209/2020-3).

Keywords: Nanotechnology; nanoemulsion; phytol; Leishmaniosis.

Testosterone compatibility evaluation with solid excipients for pellets development containing a self-microemulsifying drug delivery system

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Background: Testosterone (TST) is regulated by the hypothalamic-pituitary-gonadal axis. It is absorbed from the intestine and, if administered orally, undergoes extensive first-pass hepatic metabolism, becoming inactive. Different TST derivatives were synthesized to allow their oral administration, but they presented androgenic and hepatotoxic effects. Oral lipid-based formulations have been used to increase the oral absorption of poorly water-soluble drugs. They favor absorption by the lymphatic system, thus preventing extensive hepatic metabolism. Objective: To evaluate the interaction of testosterone with excipients for the development of pellets containing a self-microemulsifying drug delivery system (SMEDDS). Methods: The interaction between testosterone and Microcrystalline Cellulose, Croscarmellose, Crospovidone and Lactose was determined by Differential Scanning Calorimetry (DSC) and Thermogravimetry (TG/DTG). Both were performed with isolated compounds and with physical mixing with the TST (1:1 m/m). The DSC were performed using curves between 25 and 300 °C, using DSC-60 (Shimadzu, Japan), under a nitrogen atmosphere with a flow rate of 50 mL.min-1. The TGs were performed on a TGA/DTA-60 thermoanalytical balance (Shimadzu, Japan), under a nitrogen atmosphere with a flow rate of 50 mL min-1, between 25 and 500°C. For the mixtures, the compounds were weighed on an analytical balance and vortexed for 2 minutes. DSC and TG/DTG data were exported by Shimadzu's TW60S software and plotted in Origin® Pro8.5 software. Results: The DSC and TG/DTG curves of the TST and the isolated excipients showed an endothermic peak and a mass loss event similar to their melting/degradation points described in the scientific literature. In relation to the mixtures of TST with the excipients, they presented DSC Tpeak and mass loss temperatures (TG) in the same range observed for TST. No significant changes were observed in the thermal events (melting temperature and degradation) of the TST in the presence of the excipients; suggesting that there is no incompatibility between them. Conclusions: With the thermoanalytical techniques DSC and TG/DTG, no interactions were observed, in terms of incompatibility, between the drug and the excipients. Other analytical tools, such as FTIR, DRX, IST/HPLC, will be used to fully characterize the interaction between them.

Dense lamellar scaffold based on a colloidal complex of the polyaniline and biopolymers for electroactive stimulation of the myocardial

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Background: Myocardial infarction leads to ventricular remodeling, fibrosis, necrosis, heart failure, which may cause partial or total cardiac dysfunction. Tissue engineering is an approach to treat disease or damage in tissues and organs. To mimic the extracellular matrix of tissue, the architecture of scaffolds the of is one of the most critical challenges in the field of tissue engineering. The use of biopolymers associated with polyaniline, conductive polymer, might play an essential role in stimulating proliferation, adhesion, or differentiation of various cell types. Objectives: To design of an acellular cardiac scaffold that prevents myocardial wall remodeling and ultimately restores function to the heart. Methods: Briefly, the hydrogel was obtained by a mixture of collagen, fibroin solution, hyaluronic acid, and polyaniline. The hydrogel was submitted to plastic compression method to obtain the dense lamellar scaffold (DL-scaffold). The DL-scaffold was characterized by its physiomechanical properties, morphometric characteristics, electrical conductivity, cell viability (MTT method), and image cytometer. Results: The physiomechanical properties of DL-scaffolds obtained for traction strength was 2.68 ± 0.23 N, drilling strength was 1.60 ± 0.07 N, mucoadhesion strength was 1.54 ± 0.12 N, flexibility was 0.75 ± 0.05 N, and young's modulus was 1.77 ± 0.11 MPa. The DL-scaffold showed the high interconnectivity between the pores (71.06%) with anisotropic features. The electrical conductivity of the DL-scaffold was 2.10−6 S/cm2 for dry DL-scaffold and 6.10-4 S/cm2 for hydrated DL-scaffold. The cell viability of DL- scaffolds was above 90% for H9c2 cell lines, while the cell multiplication the preliminary results show that after 48 h the DL-scaffolds presented differentiated growth, with lower cell growth in the treatments. Nonetheless, after 72 h, they showed the same growth as the control, indicating normality cell cycle carrying. Conclusion: Combination polyaniline with biopolymers, appears to be appropriate to construct of a 3D structure able to be harboring native cells, to stimulate the growing, spreading, and organization for the formation of new tissue. The DL-scaffolds showed physiomechanical and physical-chemical properties supported the viability and proliferation of cardiomyocytes and repair of damaged heart tissue. Acknowledgement: CNPq n° 164479/2020-5.

Modulating liposome-cancer cell membrane interaction and cytotoxicity by fine tuning lipid composition

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Background: Liposomes are one of the most explored and versatile drug delivery systems for a large number of active pharmaceutical ingredients and different drug administration routes. Liposomes are manly constituted by phospholipids forming lipid bilayer spherical structures containing an aqueous core. Currently, there is a wide variety of lipid types available for manufacturing liposomes, both natural and synthetic, which can strongly influence their final characteristics, such as size, surface charge and membrane flexibility. These characteristics can directly impact on how liposomes interact with biological barriers and ultimately with cells. Objectives: To develop and characterize distinct liposome formulations and investigate the effects of different lipid compositions on cell viability of multiple cancerous cell lines. Methods: Four formulations were prepared, using a natural lipid, soy phosphatidylcholine (PC) and a synthetic lipid 1,2-Dimyristoyl-sn-glycero-3-phosphocholine (DMPC), with and without cholesterol (40%). Liposomes were prepared using the thin-film hydration method and followed by extrusion to obtain uniform vesicles. Liposomes were characterized by size and polydispersity index (PdI) using dynamic light scattering (DLS) and membrane flexibility using electron paramagnetic resonance (EPR). In vitro cytotoxicity against tumor cells were evaluated using the MTT assay after 24 hours of exposure to each formulation. Results: All formulations showed around 100nm diameter with low PdI. As expected, cholesterol increased membrane rigidity for both lipids. MTT results demonstrated a concentration-dependent cellular viability, however, distinct profiles were observed regarding each formulation and cellular line. Conclusion: Results indicate that distinct cell lines respond in different ways to the same formulation, depending on the liposomes characteristics and the type of structural lipid.

Liposomes structure and stability in nebulization processes towards pulmonary delivery

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Background: Nasal route is mainly used for local administration or treatment related to the upper respiratory system. However, with pharmaceutical nanotechnology advances it has also been possible to reach other parts of body through respiratory routes, such as the brain, the immune system and even the systemic route. Nebulizers are a useful and versatile device to create aerosols intended for respiratory delivery and there are basically two types: the air jet and the ultrasonic. Objectives: evaluate the structure of liposomes during nebulization process, analyzing the influence of the type of nebulizer and composition of bilayer. Methods: A customized glass impinger (GI) device was developed, mimicking the respiratory tract for testing nebulized liposomes. Soy phosphatidylcholine liposomes with or without cholesterol (Chol.) were prepared and nebulized in GI using both kinds of nebulizers. Liposomes were characterized by dynamic light scattering (DLS) for Z-average, bilayer fluidity and its possible disruption were evaluated by inserting a fluorophore molecule into liposomes for quantitation of the emitted fluorescence and Electron Paramagnetic Resonance (EPR). All analyses were performed before and after the nebulization in GI. Results and discussions: Initially the liposomes with and without Chol. presented Z-average of 99 and 114 respectively, after air jet nebulization were found to be 105 and 156, and 103 and 102 with ultrasonic nebulizer, all samples showed statistical differences except the samples with Chol. nebulized by ultrasonic nebulizer. EPR showed similar results for liposomes with Chol. integrated to the membrane, suggesting a more rigid bilayer and the fluorescence measurement gave information about liposome bilayer destabilization during nebulization, but the sample collected in “artificial lung” didn't show statistical differences when compared with initial sample. Conclusion: It's extremely important to ensure liposome vesicles stability during nebulization process to guarantee that this particle will be able to act as a drug delivery system, without losing any of its drug loading, structural or functional characteristics. The customized GI apparatus helped us to understand this process and make reliable choices regarding liposome composition when pulmonary delivery is aimed.

Development and characterization of self-microemulsifying drug delivery systems containing olanzapine

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Background: Nanotechnology has emerged as a solution to improve the efficacy and safety of many drugs. As most of new drugs present problems of solubility and low oral bioavailability, self-microemulsifying drug delivery systems (SMEDDS) is an approach to overcome such issues. Objectives: The objective of this work is to develop and in vitro characterize SMEDDS to improve the oral bioavailability of olanzapine. Methods: The interaction between olanzapine and differents lipid excipients (oils and surfactant) was determined by Differential Scanning Calorimetry (DSC) and Thermogravimetry (TG/DTG). Both analyzes were performed with isolated compounds and with physical mixture of the olanzapine with selected excipients (1:1 m/m). Pseudoternary phase diagrams were constructed using twenty different proportions of oil, surfactant and co-surfactant to obtain the areas of SMEDDS formation. 200 uL of each mixture of the different proportions of oil, surfactant and co-surfactant were dripped in 300 mL of water in a glass beaker, under magnetic stirring (20 rpm) at 37 °C, and after 5 min of stirring, they were evaluated for visual appearance, droplet size and PdI by the dynamic light scattering technique and physical stability of the formulations were investigated. Results: In the pre-formulation studies, it was possible to select mygliol, tween 80 and span 80 as excipients for the preparation of self-emulsifying systems. Proportions of 50 to 90% oil, 0 to 50% surfactant and 0 to 50% cosurfactant were used. Formulations F9, F10, F13 and F14 were the ones that presented the best visual parameters, size and PdI and remained stable during the evaluated period. After the incorporation of olanzapine, it presented an average droplet size of 179.1nm to 228nm, PdI of 0.260 to 0.486 and remained stable under the conditions evaluated. Conclusions: With the DSC and TG/DTG it was possible to select the excipients to prepare the self-emulsifying systems. SMEDDS containing olanzapine have been successfully prepared which showed the characteristics and stabilities necessary for further in vitro characterization and performance evaluation to improve its bioavailability. Acknowledgment: I would like to thank CNPQ for the scholarship opportunity.

Colorectal cancer quadruple co-culture spheroid model for evaluation of anti-angiogenic properties of nanoparticles containing bevacizumab

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Colorectal cancer (CRC) occupies the third position worldwide in terms of incidence and is the second cause of cancer-related deaths. Intravenous chemotherapy has been the therapeutic resource used in the treatment of CRC, but the limited therapeutic efficacy and adverse effects compromise the use of this route. The colon-specific release of bevacizumab (BVZ) from nanostructured systems aimed at increasing efficacy and reducing side effects has been widely explored and shown to be a potential strategy for the treatment of CRC. Still, its transposition to the clinic has not been straightforward due to the use of simplistic pre-clinical models, which do not mimic the complexity and heterogeneity of the CRC microenvironment. In this study, multicellular spheroids based on a quadruple co-culture were developed by combining epithelial colon cancer cells (HCT116), human microvascular endothelial cells (HPMEC), human intestinal fibroblasts (HIF), and monocytes, for evaluation of the angiogenic activity in the context of anticancer therapy. The three-dimensional (3D) model of spheroids presented intrinsic characteristics of the CRC tumor microenvironment (TME), such as spatial organization of cells, presence of extracellular matrix (ECM), and necrotic core in spheroids with less proliferation of endothelial cells. Uptake of the spheroid showed the presence of the four cell types by immunofluorescence and Flow Cytometry. HCT116 epithelial cancer cells constituted the majority of spheroid composition cells (93.54 ± 3.99 %), fibroblasts 2.79 ± 1.74 %, endothelial cells 2.64 ± 1.358 % and macrophages showed a small rate of 0.61 ± 0.35 %. Three nanoparticles containing bevacizumab were evaluated in the delineated models, with and without chitosan surface modification, named 2:8, OC, and LMWC. Overall, the 3D model represents a valuable model to assess the effect of nanoparticles that play a role in angiogenesis in CRC. In addition, the developed nanoparticles containing BVZ could represent a promising approach for CRC treatment.

THEMATIC AREA:

Pharmaceutical Polices and Care

Validation of an instrument for the assessment of phlebites in the tertiary health care system

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Peripheral venipuncture is the most common invasive procedure among hospitalized patients and may represent a potential risk for security incidents. Among the most common local complications of peripheral venous access is phlebitis. When not evaluated and early treated, phlebitis has a direct impact on patient safety and costs for health institutions. In this scenario, the objective of this study is to validate the content of an instrument for the evaluation of phlebitis in a high complexity hospital. This is a cross-sectional, methodological study with a quantitative and qualitative approach to the treatment and analysis of data. The Delphi technique was used, requiring two rounds of questionnaires among 24 experts and 15 experts, each round. For content validation, the Kappa indices and Content Validity Index (CVI) were applied to verify the level of agreement and consistency between experts. At the end of the second round, of the eight items of the instrument, five had substantial agreement (k = 0.63) and three had almost perfect agreement (k = 0.80 to 1.00). For the stablished minimum CVI of 0.75, all items were also approved. The instrument was validated due to global values obtained (CVI 0.90 and Kappa 0.74) and consists of an important tool with an impact on healthcare and patient safety, especially within tertiary care, in addition to promoting standardized behaviors and consequently reducing costs for the institution.

Access to medicines and pharmaceutical services for Rare Diseases: spatial analysis of the demands met in Santa Catarina

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Background: In Brazil, a disease is rare when it affects up to 65 individuals in 100,000. Despite the peculiarities of each condition, the chronic nature, the risk of life, the high cost of treatment and the low prevalence imply specific needs, such as specialized professionals and technologies for diagnosis and/or pharmacological treatment. One of the difficulties related to the management of services for rare diseases (RD) in Brazil is the absence of databases for these conditions that allows the generation of indicators and the monitoring of public policies, such as pharmaceutical services and access to medicines. Objectives: To develop a database and analyse the spatial distribution data of patients with RD in the State of Santa Catarina (SC), served by the Specialised Pharmaceutical Assistance Component (CEAF). Methods: A list of RD for the Unified Health System (SUS) was proposed and validated. From this list, the database of the CEAF operational system in SC has been analysed, based on the CID-10 registered and place of residence of the patients. The CID of the same PCDT were grouped and the prevalence rate per 1,000 inhabitants in the municipalities and health region was calculated. For the sampling of priority PCDT, the Pareto Diagram by Causes was used. The data obtained were spatialized using geoprocessing techniques, allowing analysis at different scales. Approval by the Research Ethics Committee 26186219.3.0000.0121 and 26186219.3.3001.0115. Results: 20,644 patients were identified. 12 PCDT held 81% of prevalence, including Crohn's Disease, Systemic Lupus Erythematous, Multiple Sclerosis, Amyotrophic Lateral Sclerosis and others. Two health regions presented the highest prevalence rates: Greater Florianópolis and Laguna. However, health regions with low or intermediate prevalence rates presented municipalities with prevalence rates above the State average. The distribution of specialized services does not follow the geographic distribution of patients. Conclusions: The procedure used should subsidize the health system's planning of investments in professional training, organization and availability of services in order to minimize vulnerability in the search for pharmaceutical assistance.

Assessment of trigger-tools words for screening of potential hyperactive delirium in older people hospitalized in a Brazilian emergency department

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Background: Delirium has a multifactorial etiology, leading to underdiagnose, misdiagnose and undertreatment. The use of trigger-tools has been showed an effective approach to improve detection of delirium in hospitals, which is a key quality indicator. Objective: Assess the performance of trigger-words to detect hospitalizations of older patients with potential hyperactive delirium in an emergency department (ED). Methods: A cross-sectional study was performed with all patients aged ≥60 years old hospitalized in the emergency department of a Brazilian hospital in 2018. Potential hyperactive delirium was screened with the aid of 19 trigger-words related to hyperactive delirium commonest documented in patient records. Positive predictive value (PPV) was used to assess the performance of each one. Results: Trigger-words screened 65.7% (188/286) of hospitalizations with suspected delirium. Chart review confirmed potential cases in 48.4% (91/188) of them. Four triggers showed PPV≥0.70 (hallucination, consciousness, confusion, confusional state). Agitation (PPV=0.69) and delirium (PPV=0.64) had regular performance. Conclusion: Hallucination and consciousness, despite the best performance, were less documented in patient records and might under-report the cases. Delirium and agitation may improve the identification of older people with this disorder. Trigger-tools may be associated with multicomponent strategies for screening, management, and prevention of in-hospital hyperactive delirium in geriatric patients hospitalized in the ED. The authors would like to thank São Paulo Research Foundation (FAPESP) for the scholarship grant no 2019/19430-1.

Sociodemographic, clinical and pharmacological factors associated with death in patients with COVID-19 admitted to a referral hospital

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Background: The knowledge of determinants that affect morbimortality in Coronavirus Disease 2019 (COVID-19) can provide important support for clinical and political decision making. Objectives: The aim of this study was to analyze sociodemographic, clinical, and pharmacological factors associated with death in patients with COVID-19, from a Brazilian referral public hospital. Methods: This is a cross-sectional study, with data from the hospital records of patients (≥ 18 years old) diagnosed with COVID-19, from March 2020 to March 2021. The sample was classified according to the clinical outcome into two groups: death and discharge, among which statistical associations were performed with the variables of interest with a 5% significance level. The study was approved by the Research Ethics Committee of Federal University of Alfenas. Results: Among 217 patients, factors such as advanced age, hypertension, and heart disease were associated with morbimortality for COVID-19 prior to hospital admission. The need for intensive care, use of mechanical ventilation, and total length of hospital stay was related to highest hospital mortality. Fever was among the symptoms related to death, as well as clinical laboratory testing, including lactic acid, D-dimer, markers of hepatic and renal function, C-Reactive protein, anemia, leukocytosis, lymphopenia, thrombocytopenia, pH, and blood oxygen saturation (SpO2). Medications, such as enoxaparin, dexamethasone, ivermectin, acetylcysteine, chloroquine, and clarithromycin, among others, were correlated with morbimortality. Conclusion: The outcome of COVID-19 patients was influenced by patient-related factors, such as age and comorbidities, however, therapeutic interventions and the choice of medication also impacted morbimortality. These results reinforce the need for preventive actions and adequate clinical protocols in the treatment of hospitalized COVID-19 patients.

Characterization of asthma patients attended in Winter Operations 2018 and 2019 in the city of Porto Alegre – RS

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Background: Asthma is a chronic inflammatory disease of the airways. The main cause of lack of control is poor adherence to treatment, which is related to the complexity of the use of inhalation devices. In this sense, the role of the pharmacist is essential in patient education and counseling. Objectives: To characterize sociodemographic and clinical profile of patients with asthma treated in the Winter Operations 2018 and 2019 in the city of Porto Alegre - RS. Methods: This is a descriptive, retrospective study. Data were collected from medical records and computerized system. The degree of asthma control was assessed using the Global Initiative for Asthma (GINA) questionnaire. Patients diagnosed with asthma who were attended at municipal emergency care units during the Winter Operation period in 2018 and 2019, with prescription of inhaled medications from the Municipal List of Essential Medicines of Porto Alegre (REMUME-POA) and that underwent pharmaceutical evaluation were included in the study. Winter Operation is an action promoted by the Municipal Health Department in which pharmacists, pharmacy assistants, nurses, nursing technicians and physicians are temporary hired to work in services within the Primary Care and medium and high complexity, in order to satisfy the increased demand for services in this period. The Statistical Package for Social Sciences® program (SPSS Inc., version 22) was used for descriptive analyzes. Results: In total, 129 patients were included in the study. There was a predominance of females (61.2%) and the median age was five years (0 to 89 years). According to pharmaceutical evaluation, 51.9% of patients had uncontrolled asthma and only 3.9% had well-controlled asthma. In addition, 51.9% had a prescription exclusively for relief medication (albuterol), without prescription of inhaled corticosteroids (IC). More than half (55%) had no prescription for a crisis treatment regimen. Conclusions: There was a high percentage of patients with uncontrolled disease, using only albuterol, and without prescription of crisis treatment regimen, indicating the need for training for prescribing professionals and emphasizing the importance of the pharmacist's participation in the health team for patient counseling and communication with the prescriber.

Municipal pharmaceutical care and hospitalizations for sensitive conditions primary care: is there any connection?

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Access, rational use of medicines and the quality of services provided in Primary Health Care (APS) are international discussion topic. In Brazilian territory, the actions and services of the Unified Health System (SUS) in APS and the Basic Component of Pharmaceutical Services (CBAF) are mainly the responsibility of the municipalities. One of the outcomes related to the quality of APS is hospital admissions due to conditions sensitive to primary care (ICSAP), with an inverse relationship between measures of access to care referred to as primary and ICSAP. Bearing in mind the importance of Conditions Sensitive to Primary Care, this study aims to seek answers about the relationships between Pharmaceutical Services (AF) and ICSAP in the context of municipalities covered by the QUALIFAR-SUS program. This is a quantitative ecological observational study, based on national secondary data. We analyzed 3509 Brazilian municipalities that participated in the QUALIFAR-SUS national program from 2012 to 2021. Data were collected from SIOPS, DATASUS, CNES and SIH-SUS databases: amount transferred fund-to-fund for CBAF acquisition, the number of pharmacists working in municipal APS and the number of ICSAP to prepare rates per inhabitant and per 10,000 inhabitants compiled and analyzed in Excel® software. The results found were a global average of 2.87 pharmacists for every 10 thousand inhabitants, with lower rates in the North and Northeast regions. In the data obtained from the SIOPS system, evaluating how much the municipalities received for the purchase of medicines from the CBAF, it was found that the average in the year 2020 was R$ 6.46 per inhabitant, where municipalities in the North and Northeast regions recorded lower rates. Regarding ICSAP, it was found that the highest rates were observed in the South and Midwest regions. It is concluded that the increase in the presence of pharmaceutical professionals in APS is a national reality, but there are still differences in the application of resources and even where there is a resource and presence of professionals, there is a need to investigate the relationships of the AF components with the outcomes of the ICSAP. Interventions in municipal AF require complex actions, which are essential to achieve sustainable results in the direction of better use of therapeutic resources and population health.

Pharmaceutical services in municipalities in the Amazon region

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Medicines are crucial for the resolution of health actions. For this, access needs to be more than effective, timely and equitable. Objectives: To describe the stages of adaptation and validation of indicators to assess the management capacity of Pharmaceutical Assistance (PA) in Primary Health Care in the municipalities of Santarém and Rurópolis, in the State of Pará. Methods: This is a descriptive, cross-sectional study. The protocol used as a reference was adapted to the context of the municipalities. After this step, validation was carried out with representatives of the studied municipalities, the 9th Health Regional of the State, educational institutions in the region and the group responsible for the reference protocol, using the Delphi and traditional Committee techniques. In the first phase, electronic forms were used for the individual response of the specialists. In this, the participants scored the indicators according to a Likert scale, and suggested textual changes. The forms were analyzed by the authors, the scores were tabulated in the Microsoft Excel® program and the median of each indicator was calculated. The indicator that reached a median between 4 and 5 was considered approved. A final document was prepared and taken for discussion (traditional committee), in a virtual workshop. Results: Modifications were made regarding the context, updating of legislation and an attempt to synthesize some points to increase the clarity of the analyses. The inclusion of riverside and river health units in the object of study stands out; in the logistics indicators, the verification of adaptations in the programming and acquisition of medicines considering the distances and seasonal seasons of the territories, and differences in the distribution between the units of urban, rural and riverside areas. In addition, an indicator was included that assesses the existence of actions related to the population's traditional practices in relation to health care (medicinal plants, live pharmacy and phytotherapy). All indicators had a median <4. Discussions at the workshop were based on the importance of contemplating the impact of the Amazon factor on the logistics and accessibility of PA in the region. Conclusions: The adaptation of an instrument to consider the context of Amazonian municipalities provides the recognition of their particularities and allows the analyzes carried out to support the planning of actions to overcome weaknesses in the region.

Pharmaceutical care in mental health: an experience report

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Background: Understanding the subjectivity of users of mental health services is part of the construction and professional modification necessary to meet the new demands of society. Objectives: We aim to report the experience of the discipline Practice of Pharmaceutical Education in the Community (PEFC) in two Psychosocial Care Centers (CAPS) in the interior of Sergipe. Methodology: The discipline PEFC VI, a component of the curricular structure of the Pharmacy course, developed its activities at the Psychosocial Care Center (CAPS II and CAPS AD), from August 2019 to February 2020, through the methodology of problematization with the Maguerez Arch. The students were organized into 3 classes with 10 students, who throughout the semester were able to experience once a week the activities developed among users, as well as among CAPS professionals. Results: Initially, the students drew the situational diagnosis of CAPS II and CAPS AD. Then, screening forms, pharmacotherapeutic follow-up, pharmacotherapy review, among other materials necessary for the development of Pharmaceutical Care Services, were elaborated. Thus, according to the user's need, the process of pharmaceutical care in mental health resulted in the elaboration of care plans, documentation in the medical record and pharmacotherapeutic segment, discussion of clinical cases among students and conversation circles between students, users and professionals, where health education topics were worked on dynamically. At the end of the semester, the following activities developed were counted: 94 screenings, 52 clinical cases, 52 pharmacotherapy reviews, 23 users referred for pharmacotherapeutic follow-up, 23 pharmaceutical consultations, and 23 Care Plans. Conclusion: The pharmacist needs to assume his social role acting in pharmaceutical mental health care, aiming to improve the quality of life of individuals with mental disorders. Thus, the insertion of the pharmacist in the area of pharmaceutical care in mental health will gain greater visibility, and consequently, will benefit users.

The complexity of the normative and empirical knowledge in the decision-making processes in the CONITEC

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Background: The National Commission on the Incorporation of Technologies (CONITEC) was created in 2011 to recommend the provision of medicines in the Unified Health System (SUS). Apparently, this is a rational and "normative" process by which actors absorb the available scientific evidence and issue a recommendation of the technology. However, this may be a partial picture of how the decisions may be carried out in the real world. Objective: this study aimed the construction a theoretical model involving factors that lead the execution by CONITEC in the decision-making for access to medicines. Methods: a semi-structured literature review was conducted to identify publications available in databases MEDLINE (PubMed), LILACS (BVS), ScienceDirect e Google Scholar on the positive and negative recommendations for incorporation or disincorporation of medicines conferred over the years by CONITEC. Procedure or interventions and medical devices were excluded. In conjunction with selected theories, the inductive methodology was used to explain the results founded in the literature in the first step. Results: from 20 selected articles, three categories were raised that indicates what can influence decision making: 1) the normative elements such as utilization of moderate to high level of clinical evidence by the tool GRADE, associated to low economic impact; 2) the empirical or deliberative factors such as values and principles of fulfilment unmet needs, equity in the in resource allocation, innovation of the technology and real-world adherence to the patients medicines, and others; and 3) stakeholder involved in HTA: rationalities, power structures, interests and interdependencies. Usually, all evidences interact in a non-homogeneous way with the rationality. Conclusion: The contributions of this model of analysis are increased consistency and more transparent formal process conducted by CONITEC's evaluations. In most cases, the driver's decision was based on multiple factors for the recommendation of a medicine. Emphasising the deliberative process over exclusive institutional rules can establish and improve the HTA process in the country that are appropriate to the health decisions of local contexts. Keywords: Health Technology Assessment; Government Regulation; Policy.

Cunhãs of Municipal Pharmaceutical Services in the interior of Amazonas

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Pharmaceutical Services (PS) is an instrument of the National Health Policy, ensuring access to medicines and supplies for the population. The PS involves the municipal instance in the provision of pharmaceutical services and is a challenge for the management. In Amazonas (AM) it faces challenges for the construction of public health and PS policies, where inequalities are accentuated in the 62 municipalities, the scenario is complex, demands higher quality state performance and involves challenging demands to professionals. Objective: Knowing the profile of municipal PS pharmacists in the interior of the Amazon. Cross-sectional exploratory study of quali-quantitative approach, using electronic form to collect information about the sociodemographic profile, academic background and professional practice. The support of the Department of Pharmaceutical services Policies of the ASHS enables responses in the 61 municipalities in the interior. Of the 75 responses, cunhãs (women) (73%), between 30 to 39 years old (37%), are the predominant workforce in the PS. 44% of the respondents have been working in the HF for 1-3 years; 64% have a work week longer than 30 hours, and only 12% are permanent employees. Storage, stock control, distribution and dispensing of drugs (>70%) of the services, pharmacotherapeutic follow-up, preparation of technical opinions and notes and pharmacovigilance (<10%). 88% of the pharmacists are from Amazonas and 45% work in the city where they were born, having graduated in private universities in the capital. Considering the Amazonian factor, the study contributes to understand the dynamics and permanence of the pharmacist in the municipalities, with locoregional specificities, where they develop actions and services focused on the provision of medicines and some experiences related to pharmaceutical care. These actions and services make it possible to expand the population's access to PS.

Strengthening social participation in the agenda of health policies, services, and technologies: INTEGRA Project

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Background: The INTEGRA project -Integration of Health Surveillance, Pharmaceutical Services, Science, Technology, and Innovation Policies for - emerged from the need to mobilize the population to face the health, social and political challenges experienced during the COVID-19 pandemic and, also, in the future. Objectives: Participation and social engagement strengthening in the theme, integration of health policies and practices throughout different sectors of society, and the establishment of an intersectoral and integrated network of leaders, capable of acting collaboratively to defend the development of science, public policies, national sovereignty and social control over health. Methods: The INTEGRA project promoted, in the first phase, an online course to train leaders on the public policies in question in the national territory. In the second phase, regional meetings were held to sensitize and engage society and institutions. The third phase will be the realization of the 9th Symposium and approval of an agenda for the policies integration in the Brazilian Health System. The fourth phase will promote political action in different sectors of society (nationally and regionally). Results: The training course of the first phase had 2086 inscriptions, of which 973 were enrolled and 693 were certificated at the end. In the second phase, 7 face-to-face meetings were held in the five Brazilian regions, with the participation of, around, 300 people. The didactic material developed for the first phase was published for free distribution. Phases three and four are being developed until this date. Conclusions: The INTEGRA project had wide repercussions in the national territory and is promoting the formation of leaders in the five Brazilian regions, who will collaborate with actions for the integration of the health policies involved, and integration between different sector of the society such as research institutes, public managers and civil society organizations.

Production of educational material about covid-19 focused on elderly and immunosuppressed community: a way to combat fake news

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Background: In the context of the COVID-19 pandemic, the dissemination of reliable information is one of the paths to combat the new Coronavirus. A large amount of "Fake News" has been disseminated on the internet through social media and instant messaging applications. Objectives: To use social media and graphic projects as a means of disseminating scientific knowledge about Coronavirus to groups considered at risk. Among those, elderly and immunosuppressed, especially people living with HIV and cancer, looking for centers attended by these groups to disseminate the content. Methodology: The editing, alteration, handling of images, texts and videos were done through editing software such as Adobe Illustrator, Adobe Photoshop and CorelDraw. Results: In order to be visually attractive to the target audience, the graphic pieces had striking illustrations, fonts in readable sizes for people with reduced visual acuity, in addition to having simple language that is easy to understand. All graphic and audiovisual material underwent evaluation by the scientific community before being regularly published on the social media (Instagram and Twitter) of two profiles linked to UFPE. It was also sent to profiles linked to the subjects of the study, and distributed in selected locations. The choice of locations took into account their social function in the community for people considered at risk for COVID-19 in different regions of Recife city. The approach of these centers took place initially through Instagram and later with local leaders. In total, four long-stay homes for the elderly and 3 community centers were selected and visited. The posters distributed had information about the related vaccines, warning about the effectiveness and safety and how vaccines are essential to combat COVID-19, this information being adapted for each specific case of the target groups. Conclusions: The practice of scientific dissemination developed in this project provided an opportunity to reflect on the role of the university in bringing the population closer to science. Considering this aspect and the initial visibility of the project, we conclude that there is still a lot to communicate and clarify communities about COVID-19.

Equity in financing of medicines in primary healthcare: analysis of expenditures and transfers by the Municipal Human Development Index

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Background: The financing of Pharmaceutical Policy can contribute to equity in the access to health care. The municipalities are in charge for providing medicines for the primary health care, using a fixed resource from the Ministry of Health (MH) and from the States governments, plus their own resources. But, the municipalities capacity in financing the growing medicines costs can lead to an unequal access to medicines. Objectives: To analyse the evolution of municipal's investments in medicines for primary healthcare. Methods: This is an exploratory, retrospective study, in which the evolution of the per capita values in the financing of medicines in the municipalities between 2016 and 2020 was compared. Data on the amounts of the MH's contribution transferred to the municipalities were collected from the National Health Fund, and those on population, total spending on health, and percentage of spending on medication were extracted from SIOPS. The amounts invested were deflated for Dec/21, using the annual variation of the Broad National Consumer Price Index. Based on these data, analyses were made of the evolution of investments in medicines by the municipalities and their asymmetries by population stratum and by range of the Municipal Human Development Index (HDI). Results: The research identified that the increase in the per capita value invested by the municipalities, between 2016 and 2020, is well above the increase in the value of the Union's transfer, regardless of population stratum and HDI stratum. On average, the municipalities increased by 35.20% the value of investment in the acquisition of medicines, while the Union increased 14.71% (for a value of R$ 5.85 per capita/year) and there was no correction in the value of the states. The study identified that the small municipalities with lower HDI values were the ones that presented the greatest increase in per capita investment in medicines, i.e., the ones that had to pay the most for access costs during the period. Municipalities with a population between 25,001 and 50,000 inhabitants and a "very low" HDI have presented an increase of 108% in investment during the period. Conclusions: Despite the corrections in the value of the Pharmaceutical Basic Component counterpart by the MH in 2017 and 2019, the current form of financing for municipalities continues to bring impacts to the less favored municipalities, as these are the ones that are suffering the most from the increasing costs of medicines.

Diagnosis for qualification of care and surveillance of acute and chronic poisoning in the Brazilian Unified Health System

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Toxicological Information and Assistance Center (CIATox) are public units that provide assistance, technical support to professionals and health surveillance regarding cases of intoxication and promote education. Objectives: Composition the diagnosis of CIATox in the context of toxicological assistance and surveillance in the Unified Health System.This study was carried out in 2021, through interviews,using the SurveyMonkey® software, considering items of the management, structure, assistance employees, surveillance, results and education. Results: All CIATox classify cases according to severity and follow them up to the outcome, 84% of CIATox attend 24h, daily and in person. 66% perform teleservice and presential monitoring with the hospital team in charge of the service, 36.3% perform only teleservice and 18% directly assist patients. 54% have a number diferent than 0800 line, 48% of lines are connected to Anvisa and 27% have their own 0800 line. 84% and 63% of CIATox access the Toxbase and Micromedex information bases. The CIATox teams are diversified, include undergraduates and residents who perform internships and/or shifts. 18% of CIATox have their own laboratory. 69% of the Centers register the service data on Datatox system and 21% register manually 36% of CIATox notify the Notifiable Diseases Information System by Epidemiological Surveillance.There are Centers that carry out surveillance and health education and produce scientific materials. Financial management takes place by health departments, universities where they are based or shared. 60% are denominated according with Ordinance 1678/2015. 36% have records of consolidation of their creations and 45% have their own National Register of Health Establishments. and 48% admit that they are included in the emergency network. Conclusion: This study will contribute as a guide to the transformation needs of CIATox and qualification of toxicological assistance in the SUS. Keywords: toxicology; pharmaceutical care; health assessment; diagnosis of the health situation

Brazilian market evaluation of drugs available for the pediatric population up to 6 years of age

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Background: The discussion about the most appropriate dosage forms for each age group is still fragmented and not widespread.1 However, liquid dosage forms for oral use are essential for drug treatment in the pediatric population, as they are easy to administer and allow drugs to be have their dose adjusted, meeting the needs of the child's physiological stage of development and/or the aggravation of the disease.2 Objectives: Evaluate the Brazilian pharmaceutical market in what has been offered to the pediatric population up to 06 years of age. Methods: A descriptive and qualitative study was carried out on the medicines registered in Brazil, intended for children, through a search on the list of reference medicines of ANVISA3, included until August, 2020. Therefrom, all their professional package inserts were evaluated regarding the indication of use to children under 6 years of age, when children develop better swallowing skills. Results: From 2,148 pharmaceutical presentations registered with ANVISA, the analysis of the indications of the professional package inserts allowed us to identify that 774 (36.3%) presentations have an indication for pediatric use up to 12 years. Up to six years of age, the pediatric population had 417 (53.9%) presentations of reference drugs, mostly in parenteral and oral solid forms. Conclusions: There was a limitation in the number of drugs in dosage forms suitable for the pediatric population, which may lead to the need to use parenteral drugs, therefore ambulatorial use, or off-label use in order to meet children's dosage needs.

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Development and validation of the Medication Literacy Test for Older Adults

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Background: Medication literacy (ML) encompasses the skills to access, understand and act on medication information. Aging-related changes impact ML, making older adults more prone to drug-related problems. Objectives: To develop and validate an instrument to measure ML in older adults. Methods: The instrument was developed in multiple stages. A scoping review was performed to explore the construct and develop a conceptual model for ML. The instrument was generated and submitted to content validation by experts and the target population. It was applied to 228 older adults (≥60 years) selected in the community and in two outpatient services of two teaching hospitals in Belo Horizonte for psychometric validation. Results: Four, two and one-factor solutions were tested in exploratory factor analysis, which pointed to the one-dimensionality of the instrument; all items had a factor loading >0.30 in the one-factor solution. A three-parameter logistic model was adopted in the item response theory; 1 item had discrimination scores <0.65 and 3 items had guessing scores >0.35, which were excluded from the instrument. The final version of the instrument, with 28 items distributed in 08 fictitious medication-use scenarios, had excellent internal consistency (Kuder-Richardson formula 20 = 0.90). Its scores were highly and directly associated with health literacy and educational level, pointing to its convergent validity. A preliminary standardization was carried out using the percentile norm, classifying the scores as low, medium, and adequate level of ML. Conclusions: The instrument was psychometrically adequate to measure the ability of older adults to access, understand, communicate, calculate, and evaluate medication-related information. It can be used to propose actions for the safe and effective use of medications by older adults.

Development of a patient prioritization tool for hospital clinical pharmacy services

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Background: Assessment tools to indicate a need of patient prioritization have been developed because effective and efficient methods to identify high risk patients for targeted Clinical Pharmacy Service (CPS) are essential in hospital pharmacy. Objectives: To describe the development, content validation and standardization of a patient prioritization tool for hospital clinical pharmacy services Methods: The tool was developed using multiple steps: Scoping review to identify prioritization criteria/sub-criteria; Delphi technique to obtain consensus under the identified criteria/sub-criteria; Survey with pharmacists evaluating applicability of the criteria/sub-criteria obtained from Delphi; Definition of criteria/sub-criteria to be included in tool/attribution of scores. Content validation was performed by a panel of experts evaluating relevance, feasibility, clarity and adequacy of the score. Content Validity Index (CVI) was calculated. Standardization occurred through a retrospective observational study carried out at 24 and 72 hours and median of the patient's hospital stay. An intragroup norm was performed, determining percentile ranks of the instrument's total scores. Patients with a P90 score were classified with a high level of prioritization for CPS. Results: The tool is divided into three sections, with prioritization criteria for health issues; therapeutic classes; laboratory parameters. It comprises 51 criteria with specific scores with simple total calculation. None of the criteria presented CVI < 0.78, maintaining the items from the initial version of tool. The scores were adjusted per suggestions from the panel of judges. Data were collected from 393 patients eligible for the study. The P90 percentile in the three hospitalization stages (24 hours, 72 hours, and median) was found, respectively, in the following scores: 18.0, 20.0, and 22.6. Conclusions: The tool is a comprehensive and target to prioritize adults patients most likely to benefit from CPS. Evidence for adequate content validity was provided. However, further validation is necessary to establish tool performance.

Pharmaceutical Service in the prisons: a review

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Background: The prison population is affected by complex health problems, with high rates of infectious diseases and mental health disorders. These conditions require pharmacological therapies and Pharmaceutical Services has a strategic role, being essential in the articulation between management and clinical activities, with a focus on the patient, for the resolution of health problems. Objective: Analyze available information on Pharmaceutical Services in the prison context. Methods: Literature review with consultation in the National Library of Medicine (PubMed) and Scientific Electronic Library Online (SciELO) databases, carried out during July 2022. The MeSH descriptors used were: “prison”, “correctional health care”, “pharmacist”, “pharmaceutical services” and “pharmaceutical care”, using the Boolean operators AND and OR to combine the terms. Studies published in the last ten years (2012 - 2022) that addressed Pharmaceutical Services in the prison system were included, with no restriction on language. Duplicate articles and reviews were excluded. The articles were selected based on the initial evaluation of the title and abstract. Results: Eleven articles were included based on the established criteria. The studies focus on European countries and the United States. Only 1 of the studies was conducted in Brazil and points to failures in the access and rational use of medicines by detainees. Few pharmacists work in the prison system. Penitentiary agents often carried out the distribution of medicines to inmates. When performed, Pharmacist interventions were effective in improving clinical outcomes, especially in conditions such as HIV and diabetes. Conclusions: Inmates have the right to health, and comprehensive care is important given the vulnerability of this group. However, Pharmaceutical Services are still incipient in the context of prison health, especially concerning pharmaceutical care, and the development of more comprehensive studies and actions aimed at this theme is relevant.

Pharmaceutical Care in the Management of Leprosy: A Scoping Review

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Background: Leprosy is a chronic infectious disease of slow evolution, whose etiologic agent is the bacillus Mycobacterium leprae. Given their social stigma, difficult treatment and trend of occurrence of drug-related problems (DRP), the pharmacist's role in care tends to be strategic and recommended. Objectives: To describe the pharmaceutical services aimed at leprosy patients described in the scientific literature, as well as their reported impacts, whether clinical, economic or humanistic. Methods: This is a Scoping Review, the search for articles was performed in electronic databases using MeSH/DeCS descriptors in English, Portuguese and Spanish. The inclusion criteria adopted were articles, theses, dissertations or conclusion works with studies published in the last 10 years. Studies that did not focus on pharmaceutical care and/or leprosy management were excluded. Results: A total of 3,444 studies were retrieved from the selected databases and, after stages of analysis of titles, abstracts and text, 14 articles were selected. The clinical services and actions most performed by the pharmacist in the identified studies were “health education”, “interventions focused on treatment adherence”, “dispensing”, “cost reduction interventions” and “pharmacotherapeutic follow-up”. Conclusions: In the analysis of results, it was observed that pharmaceutical care actions have the potential to reduce DRP (up to 96%), improve adherence (up to 97%), improve the level of knowledge about the disease (ranging from 51% to 89.6%) in addition to the potential cost savings and improved quality of life for patients. The need to invest in new studies with this theme was evident, since only seven of the fourteen articles selected had an impact analysis with patients.

Clinical guidelines for common health problems in community pharmacies: impact of pharmaceutical training

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Introduction: About 88.5% of medicines dispensed by pharmacists are over-the-counter medicines and around 52% of patients turn to the pharmacy in search of solving self-limiting health problems. The use of clinical guidelines is an important strategy for qualification and standardization of pharmaceutical work and aims to advise professionals in the evaluation of signs, symptoms and patient orientation. Objective: To analyze the effectiveness of a training course for pharmacists on the management of self-limiting health problems.Methods: The study took place through the standardization of clinical guidelines for the management of self-limiting health problems and training of community pharmacists and students during a supervised internship in Community Pharmacy. The effectiveness of the course in the acquisition of knowledge of the participants before and after the training was evaluated. The evaluation was carried out by comparing the performance in the final and initial knowledge assessment of the participants, which consisted of 60 questions that dealt with the themes of clinical guidelines and reproduced common situations of care in the pharmacy (clinical cases). Satisfaction with the course, motivation and degree of confidence to meet the demands of pharmaceutical care were also blindly evaluated. Results: Sixty-six participants were selected, of which 59 were approved and 7 failed. The average performance in the initial assessment (pre-course) was 28 correct answers, while the final one was 46 correct answers (post-course), indicating a 60% increase in the number of correct answers, demonstrating a significant increase in knowledge after the training was completed. with the guidelines. Participants reported performing, expanding and qualifying patient care steps during training. Specifically, 90% of the participants reported being able to perform reception steps (90%), pharmaceutical anamnesis (90%), health education interventions, pharmacological interventions 78%, identifying warning signs (95%), monitoring clinical parameters (74%) In the satisfaction analysis, about 90% of the participants declared themselves satisfied or very satisfied, 97% considered the guidelines produced necessary or very necessary for their day-to-day care, 53% felt confident and 35% very confident in the care of patients with these health problems. Conclusion: The results show the effectiveness of the course in training pharmacists to manage self-limiting health problems.

Pharmaceutical policy, health regulation and technological development: analysis of Brazilian public policies in the 2003–2019 period

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Health surveillance comprises the health regulation of activities related to the production/consumption cycle of goods and services of public health interest. Its actions and practices are part of the national health policy and are inherent to the country's Unified Health System (SUS). The Brazilian pharmaceutical sector lacks the technological competences and new development strategies to meet the demands of the SUS. Overcoming the sector's limitations requires an intersectoral set of measures by public institutions, including the adoption of new regulatory practices that permeate the relationships between the national regulatory authority and the sectors it regulates. In this context, the role of the National Pharmaceutical Policy (PNAF) stands out, as it guides other sectoral policies, including those related to technological development and health surveillance. Therefore, in light of this premise, it seems vital to identify and analyse the interfaces between health regulation policies and technological development for the production of medicines of interest to the SUS, primarily in order to contribute to the reduction of the system's vulnerabilities and to the expansion of the population's access to medicines. The objective of the present study involved the identification and analysis of the interfaces between Brazilian health regulation and intersectoral policies aimed at the development, internalization of technologies and production of medicines of interest to the SUS. The study was carried out through documentary research, with the adoption of the model proposed by Walt and Gilson (1994) for the analysis of health policies. The study covered the period involving the formulation and the 15-year implementation of the PNAF. Ten public macro policies were identified with important interfaces between frameworks and regulatory practices and initiatives to stimulate technological development for the national production of medicines of interest to the SUS. The stimulus to the development of the Health economic-industrial complex boosted the definition of new milestones and new regulatory practices related to the internalization and development of technologies, maintaining interfaces with the guiding capacity of the PNAF on sectoral policies aimed at expanding the population's access to medicines.

Implementation of a Clinical Pharmacy Service in a South-Brazilian Pharmacy training unit: preliminary stage.

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Implementation science is a field that relates the transfer of evidence-based knowledge into practice. The implementation of a new service involves a diagnostic phase, the intervention itself and post-implementation. The aim of this study was to establish the historical and sociopolitical context, as well as the guiding principles and values for the implementation of services at the Pharmacy School UFSC (Faculty of Pharmacy of the Federal University of Santa Catarina). The methodology was documental analysis and consensus meetings with the team and experts. In 1985, the student political movement claimed a laboratory for teaching pharmaceutical practice. In 1987 the School Pharmacy was founded and since then, it has gone different service models, including a partnership with the private sector and with government institutions for dispensing medicines made available by the Unified Health System (SUS). As of 2022, a new service is under construction, in partnership with the Santa Catarina State Health Department. The service wil provide clinical pharmaceutical care for patients who receive medication through the court system. Given the exposed context, principles and values of the SUS are adopted as consequence, as reaffirm the rights enshrined in the Brazilian Constitution. Other guiding principles adopted are to ensure participatory management and decision-making, horizontal and transparent communication; development and application of creative and innovative technologies in pharmaceutical services and education; science as the central foundation of pharmaceutical practices; management as a technical, political and social process; ethical and respectful treatment of patients, students and workers; respect for diversity of gender, race and LGBTQIA+. The next steps are the implementation itself. Is expected that the results of the implementation evaluation will contribute to the development of tools for health planning and management.

Brazil and Colombia: health registration, incorporation into the health system and judicialization of biological medicin

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Introduction: Regulatory agencies are responsible for the health registration of medicines as a means of ensuring safety, efficacy and quality of medicines supplied in the country. In Brazil, this responsibility is held by Anvisa and in Colombia by Invima. Objectives: Analyze health registration, incorporation into the health system and judicialization of biological medicines in the period from 2012 to 2017 in Colombia and Brazil. Methods: Research in the Anvisa and Invima databases and in the judicialization database of Santa Catarina and Colombia, in the period 2012-2017. Results: The biological medicines market in Brazil resembles that in Colombia regarding the main registered products. The main dominant companies in the market are also similar in both countries, however, Brazil has government companies. Despite the accessibility strategies adopted by these countries, judicialization has become an access pathway when their health systems are unable to meet the users' needs. Judicialization has exerted pressure towards the incorporation of medicines into health systems, including the possibility of price negotiation. On the other hand, our results point to situations in which, when the medicine for a disease is already incorporated, new indications are demanded in court. The biological medicines permeate the discussion on the treatment of rare diseases. In Brazil, since the implementation of the National Policy for Rare Diseases, there has been an increase in the availability of such medicines on the market. Colombia still awaits a differentiated financing system for this category. Conclusions: The present study shows that both regulatory policies and health technology incorporation policies are highly influenced by the pharmaceutical market and by judicialization. The increased judicialization has demonstrated a risk to the sustainability of health systems because of the great financial impact caused. This means a health risk in the case of medicines without registration in the country and a disruption in terms of equity, as is the case with analogue insulins.

Brazil and Colombia: two examples to probe the reflection on the judicialization of access to medicines

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Introduction: Access to medicines is a right to health, and also considered a social good, whose purpose is prevention and resolution in health. Currently, all health systems face the challenge of ensuring access to medicines, especially those with higher prices. The concern with the sustainability of public policies and, consequently, of health systems is a constant, especially in scenarios where judicialization has become an alternative way to access these medicines. Objectives: To reflect on the judicialization of medicines in Colombia and in the state of Santa Catarina. Methods: Analysis of lawsuits filed against the state of Santa Catarina and requests for reimbursement for health technologies provided by court order of the contributory regime of Colombia between 2012 and 2017. The data from Colombia were provided by the Resource Manager of the General Health Social Security System (ADRES). For the analysis, the model proposed by Vargas-Peláez (2016) was considered. The two countries have important differences in the health system model, but both have public policies to guarantee access to medicines, through systematic processes of incorporation of medicines. In both countries the phenomenon of judicialization has acquired worrying proportions. The two countries have taken different measures to face the phenomenon. Lawsuits for access to medicines have significant differences in profile. Conclusion: The study generated useful information for managers' decision-making and identified that the dialogue between public policies, managers and health services are fundamental in facing judicialization.

Importance-performance analysis of an interprofessional curriculum component in undergraduate health courses

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Background: an interprofessional course (IC) was developed at a university in southern Brazil. Its elaboration came from "PET-Saúde", a government program created to promote teaching-service-community integration. Interprofessional groups of Physical Education, Nursing, Pharmacy, Medicine, Dentistry, and Psychology students developed activities in the municipal health system. The IC was mandatory in the curricula. Objective: the study aimed to investigate experiential in-service learning through importance-performance analysis (IPA) by undergraduate students. Methods: quasi-experimental study, with pre and post-test of students exposed to the interprofessional education approach to developing collaborative competencies. The IPA was associated with the SELEB scale. In the importance analysis, we applied a 12-item questionnaire, involving organizational skills, social self-confidence, and work skills. At the end of the course, we used an analogous performance questionnaire, with 20 items. Both questionnaires used Likert scales. Cronbach's alpha test estimated the scale reliability. The statistical analysis (StataIC 14.2® software) used the Wilcoxon test for paired samples to compare the differences between the averages. Results: The study was in 2019. In the pre-test, 174 students participated and 194 in the post-test. The mean importance of practical skills reduced from 4.50 to 3.49 in performance, with a significant difference (p < 0.0001) and mean effect size. The average of all the variables of the SELEB scale decreased in the attribution of performance in relation to importance. The variables "Understanding cultural and racial differences" (Spearman's Rho= -0.2702; p=0.0008) and "Social responsibility and citizenship skills" (Spearman's Rho= -0.2369; p=0.003), category "Citizenship", showed an inverse correlation with students' income in the dimension of importance. The SELEB scale showed excellent internal consistency (Cronbach's alpha = 0.9187). Conclusions: Even with the reduction in the SELEB scale between importance and performance, all variables showed a great learning effect, indicating effective experiential learning. Students considered interdisciplinarity important. They expressed high performance in it. "Ability to work with other people" was the highest performing competence. This is essential for collaborative health practice. The pedagogical strategy showed promising results for interprofessional education.

THEMATIC AREA:

Pharmaceutical Technology

Do the HPMC substitution pattern and plasticizer features affect the mechanical properties of needleless anesthetic delivery systems?

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Background: The overall technological development of a needleless mucoadhesive drug delivery platform based on polymeric thin films requires the evaluation of the features related to the manufacture and scale up, such as the elasticity, plasticity, flexibility, and mechanical resistance.Objectives: To use Quality by Design approaches for evaluating the effects of HPMC substitution pattern (HPMC E15 LV and K100 LV; 3% m/m); plasticizer's (glycerol, mannitol and PEG400) molecular weight, hydrophilicity, and loading (0.0, 0.12 and 0.24% w/w) on the mechanical properties of dental anesthetic films.Methods: Thin films (n = 10) containing aminoamide salts (1:1, 47 mg/cm2) were obtained following a factorial design of experiments mixing two and three level. The mechanical properties of the films were evaluated using a tensile modulus TA.XT plus texture analyzer according to ASTM D882-Method 02 (50 Kg load cell; test speed of 1 mm/s; maximum elongation of 190%). The analyzes (n ≥ 5) were performed at 25 ± 2 ºC. From the stress x strain curves, we determined: tensile strength (TS, MPa), elongation at break (E, %) strength at break (FB, N), and Young's modulus (Ym, MPa). Complementary multivariate data analysis toolset (i.e., Response Surface Methodology, Principal Component Analysis and Correlation Matrix) has been used to clarify the effects of the studied factors. Results: The plasticizer loading was the main factor affecting the TS, E, FB and Ym; while neither the methoxyl or hydroxypropyl substitution degree of HPMC, nor the hydrophilicity descriptors of plasticizers played significant roles on such mechanical properties.Conclusions: Irrespective of HPMC type and physicochemical features of the hydrophilic plasticizer herein studied, increasing the loading of plasticizer makes films less resistant, more plastic, and more flexible.

Iontophoresis of dacarbazine for topical treatment of skin cancers

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Dacarbazine is the drug of choice for the treatment of melanomas. Like any other chemotherapeutic drug, its systemic use brings numerous toxic side effects, which could be avoided with a more localized, topical therapy. However, topical skin delivery of the drug would be challenging, considering that therapeutic levels of such a polar molecule may not be achieved upon a passive topical application. In this way, this work aims to verify the influence of iontophoresis, a non-invasive energetic technique, on dacarbazine skin delivery. For this, Franz-type diffusion cells were mounted with porcine skin separating the donor from the acceptor compartment, which was filled with 15 mL PBS and maintained under magnetic stirring at 32 ºC. The donor compartment was filled with 0.1% (w/v) dacarbazine in PBS, and current densities of 0.12 or 0.50 mA/cm2 were delivered to the solution. A passive experiment was also performed as a control. Hourly, 1 mL PBS was withdrawn and taken to HPLC for drug quantification. After 5 h of the experiment, the skin was removed from the diffusion cell, cleansed, and the stratum corneum (SC) and hair follicles (HF) were separated from the remaining skin (RS) by differential stripping. The drug was extracted from each skin layer and taken for quantification too. Both current densities increased the penetration of the drug into the SC by 4-fold (p<0.05) compared to passive delivery. In contrast, the drug recovered from the HF was not different (p>0.05) among the three evaluated conditions. For the RS, the 0.50-mA/cm2 electric current enhanced 8- and 9-fold (p<0.05) drug penetration compared to passive and 0.12-mA/cm2 electric current. Furthermore, cathodal iontophoresis also stimulated the transdermal delivery of the drug in a current-dependent fashion. Thus, cathodal iontophoresis proved to be a promising alternative to promote and control, in a non-invasive way, the cutaneous penetration of dacarbazine, enabling a future use in the topical treatment of cutaneous tumors.

Emulsion containing thyme and oregano essential oils associated with antimicrobial activity against Staphylococcus aureus causing bovine mastitis

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Mastitis is a multifactorial disease resulting from the interactions between cattle, microorganisms, and the environment. Mastitis can have adverse effects on animal and human health, an important issue to address the One Health approach currently. The administration of synthetic antimicrobials by the intramammary route is the treatment of choice for mastitis. However, there are numerous reports of the emergence of multidrug-resistant strains of Staphylococcus aureus that cause mastitis. In this work, thyme (TEO) and oregano (OEO) essential oils associated were incorporated in emulsions based on poloxamer 407 polymer. The in vitro antimicrobial potential of the formulations on strains of S. aureus - ATCC 25923 and clinic isolates collected from bovine mastitis were researched. Emulsions containing poloxamer 407 at 20% w/w were prepared by ultra homogenizer. The associated EOs were incorporated at concentrations of 2.5, 3.5, 5, and 10% w/w; TEO and OEO ratio was 89 and 11%, respectively. The proportions of associated EOs were defined in a previous studies. The preliminary physical stability of the emulsions was evaluated through pH, thermal, and mechanical stress tests. The best concentration of associated EOs was defined by the microbiological assay using the ATCC strain. The antimicrobial effectiveness of the emulsion containing the chosen concentration of the associated EOs (10% w/w) was evaluated on clinical strains, sensitive and resistant to synthetic antimicrobials. All formulations remained stable, without phase separation, for all stress test conditions studied. The incorporation of EOs decreased the pH of the base emulsion without alterations after the stress tests. The formulation containing the EOs associated with 10% w/w was effective at inhibiting the growth of all clinical strains of S. aureus. The results suggest that the formulation shows potential for it's intended use. Physicochemical and microbiological quality attributes of the formulation kept in different storage conditions will be investigated over time.

Development of a mucoadhesive film loaded with curcumin for topical treatment of oral tumors

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Background: Curcumin (CUR) is one of the main substances found in the Curcuma longa rhizome and has been studied to treat various carcinoma types. However, therapeutical use of CUR has some disadvantages, such as poor oral pharmacokinetic, mainly due to its low water solubility and sensitivity to physiological pHs. Thus, in the case of superficial tumors, such as oral cancers, its topical use from a formulation that guarantees therapeutic concentrations of the drug reach the affected site would be an excellent alternative. Objective: The objective of this work was to prepare a mucoadhesive film containing CUR as an effective alternative for the topical treatment of oral cancers Methods: A film composed of polyvinyl alcohol, chitosan, and propyleneglycol was prepared by oven drying and characterized regarding its average weight, thickness, pH, CUR content, tensile force to disruption, and mucoadhesivity. Drug release from the film to a physiological media was then accessed in vitro over 24 h. In vitro permeation of CUR from the film compared to a control (CUR solution) was determined using porcine mouth mucosa mounted in Franz diffusion cells. Results: The obtained film was yellow, flexible, bubble-free, and crack-free. It presented average weight of 2.36 ± 0.06 g, thickness of 0.25 ± 0.01 mm, pH of 5.5 ± 0.1, and CUR content of 66.8 ± 17.2 µg/cm2. It was also resistant (tensile force to break = 1750.5 ± 108.6 g) and mucoadhesive once the force required to separate the mucoadhesive film from the buccal mucosa was measured to be 9.9 ± 0.7 g. Release assays demonstrated the drug was progressively released to physiological media from the film. Finally, in vitro permeation studies showed that the film enhanced CUR penetration in the oral mucosa by 1.7-fold (p<0.05) compared to the control. Conclusions: Remarkably, the film containing CUR is mucoadhesive and not only increase the drug permanence time at the site of administration but also enhance CUR delivery to the mucosa. It should, therefore, be a promising alternative to the topical treatment of oral tumors using this natural drug.

Film forming systems containing pomegranate peel extract for mastitis prophylaxis: physicochemical and biological in vitro evaluation

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Diseases caused by bacterial infections in small-scale and industrial livestock are becoming a serious global health concern in veterinary science. Mastitis is one of the most costly pathologies and *Staphylococcus aureus* is the main etiological agent. The objective of the present work was to develop polymeric *in situ* film forming solutions (ISFFS), containing pomegranate peel extract (PPE), for use as an antiseptic in the prophylaxis of mastitis. The use of PPE can help to minimize the problem of microbial resistance to conventional synthetic antimicrobials. To this end, four polymeric blend formulations of ISFFS containing different proportions of poly(vinyl alcohol) (PVA) associated or not with sodium polyacrylate (SPA) were developed. The PPE was incorporated in these blends at concentrations of 1.25, 2.5 and 3.75% w/w. The most promising concentration in blends was defined after *in vitro* microbiological analysis by the modified disk diffusion method against *S. aureus* ATCC (25923) strains and clinical isolates from bovine mastitis. In the most promising formulation (PPE at 2.5% w/w), physicochemical tests were carried out in the blends, namely: description, pH, viscosity, total phenols content (TPC) and drying time on the skin. Thickness, average weight, residual moisture content (RM) and hemolysis index (HI) were evaluated in films containing PPE formed by the best blends. There was no statistical difference between the inhibition halos formed at the concentration of 2.5% w/w for the others. Antimicrobial activity was observed for the different blends containing PPE at 2.5% w/w against all clinical strains isolated from bovine mastitis, sensitive, and resistant to synthetic antimicrobials. As the TPC present in the PPE are the main responsible for its antimicrobial action, the formulation with the highest content of these compounds was chosen as the most promising. The chosen ISFFS containing 18% PVA, 0.50% SPA, and 2.5% w/w of PPE, presented a TPC of 82.80% in relation to the incorporated PPE; viscosity of 374.40 cP; pH 5.81; and, drying time of 29 min and 25 s. Its films showed uniformity in the parameters of average weight and thickness; 15.52% of RM; and were considered slightly hemolytic, with a HI value of 4.52%, being considered hemocompatible. Complementary analyzes to evaluate the composition, compatibility and stability of the PPE in the films will be carried out by Fourier transform infrared (FT-IR) and thermal analysis methods.

Inclusion complex of spiro-acridine derivative AMTAC-02 with 2-hydroxipropril-β-cyclodextrin: Preparation and characterization

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Background: The new spiro-acridine compound (E)-1-((4-methoxybenzylidene) amino) -5-oxo-1,5-dihydro- 10H spiro[acridine-9,2-pyrrole] -4- carbonitrile (AMTAC-02) showed selectivity towards the topoisomerase IIα enzyme and antiproliferative activity. However, high lipophilicity causes limitations for its therapeutic use. The use of cyclodextrins in the formation of inclusion complexes with hydrophobic drugs allows to increase apparent solubility and stability. Objective: Develop and characterize an inclusion complex with AMTAC-02 and HPβCD. Methods: Phase solubility study for the AMTAC-02/ HPβCD was carried out following the method described by Higuchi and Connors. The apparent stability constant (Ks) was calculated from the linear relationship between the molar concentration of AMTAC-02 in the solution medium as a function of the HPβCD molecular concentration. The inclusion complex was prepared by freeze-drying method, the HPβCD and AMTAC-02 were weighed accurately at a 1:1 molar ratio and dissolved in distilled water on shaking for 72 hours at 25°C. The solution was frozen and lyophilized for 24 h. The morphology of inclusion complex was investigated for scanning electronic microscopy (SEM) (Tescan, model VEGA3 SBH).The X-ray diffraction (XRD) patterns for pure AMTAC-02, HPβCD, AMTAC-02: HPβCD inclusion complex, and the physical mixture were acquired using a diffractometer (D8 Advance, Bruker, EUA) with CuKα radiation. The scanning rate employed was 2°/min over a diffraction angle of 2θ in the range of 5–50°. Results: The phase solubility diagrams showed that the concentration of AMTAC-02 increased with the increase of HPβCD concentration. The diagram obtained can be classified as AL type suggesting that the formation of 1:1 complex between AMTAC-02 and the HPβCD and the Ks value was 724.470 M^{-1} indicating the strong interaction between HPβCD and AMTAC-02. The SEM showed inclusion complex exhibited an amorphous structure different from the materials isolated, indicating the possible formation of inclusion complexes between HPβCD and AMTAC-02. The XRD results suggest that raw AMTAC-02 was not present in the form of crystalline after complexing with HPβCD, but rather existed in a semi-crystalline state. Conclusions: The inclusion complex was successfully obtained. Future studies will be carried out to characterize the inclusion complex's physicochemical and effectiveness.

Development of biodegradable ocular implant containing Punica granatum L. fruit extract for neovascularization inhibition in diabetic retinopathy

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Background: The neovascularization is a pathological process in Diabetic Retinopathy (DR) which can cause visual impairment and blindness. To control this deregulated angiogenesis treatment options includes intravitreal administration of antiangiogenic agents, decreasing patient adherence to treatment. The search for new medicines and routes of administration in the treatment of retinopathy has been of great interest. Objectives: Develop a biodegradable implant with fruit extract of *Punica granatum* (pomegranate) for intravitreal application aiming to control neovascularization in DR. Methods: The pomegranate (SisGen A2FA1FC) was collected, dried, pulverized and subjected to decoction. Phytochemical screening in CCD was performed and the quantification of total polyphenols and tannins was performed using Folin Ciocaulteu. The implants were prepared by dissolving aqueous extract (PAE) and PLGA 50/50 in ACN at ratio of 1:3. The solution was lyophilized and powder obtained was molded into cylinders at 70-90°C. The degradation of the implants was evaluated *in vitro* for 60 days and implants, analyzed by scanning electron microscopy (SEM). Antiangiogenic activity of PAE solution and PAE released from implants was evaluated in chicken chorioallantoic membrane (CAM) assay. Results and Discussion: PAE had 33% of hydrolysable tannins. Implant *in vitro* degradation was observed by loss of mass: 7% in 7 days, 19% after 21 days and 54% after 35 days of experiment. It was not possible to accurately weight the remaining implant mass at the end of 60 days. The progressive erosion of polymer matrix was observed by SEM images, suggesting a gradual release of the active over 60 days. The PAE and PAE implant showed an antiangiogenic activity in CAM model equivalent to Bevacizumab® (BVZ), an off-label drug already used to treat neovascularization. The BVZ (6.25 mg/mL) caused a reduction of 57% in the formation of new blood vessels, while PAE (2.5 mg/mL) and the implant (25% PAE) reduced neovascularization by 33 and 53%, respectively. Conclusion: The implant with PAE reduces significantly the angiogenesis and data suggest a prolonged release *in vitro* model. Thus, PAE implant may be a promising alternative control neovascularization in the retina.

Development of liquid-crystalline gel based on amazonian butter for treatment of vaginosis

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Liquid-crystalline drug delivery systems have organized structures that combine liquid and solid states, which ensure the incorporation of drugs with different properties, in addition to promoting sustained release. The use of products based on plant raw materials has potential technological advantages in the development of biocompatible and biodegradable delivery systems. Therefore, the aim of this work is to develop a gel based on butter extracted from ucuuba seeds for the treatment of vaginosis. To prepare the formulations, the ucuuba butter was heated to 40 ºC, and mixed with the surfactant, palm kernel oil, water and metronidazole. All formulations were characterized by Polarized Light Microscopy (MLP). Validation of the analytical method for drug quantification was performed by spectrophotometry. Swelling assay and in vitro drug release studies were assessed using the dialysis method. The analytical method was accurate, with a relative standard deviation (RSD) of 0.53% for intra-day and 1.10% for inter-day precision. The drug recovery rate was 92% (RSD < 5%). After characterization by MLP, the formulation showed a hexagonal phase. In the swelling test, the formulation captured 40% of water in 8 h and became more viscous, showing a slower profile for drug release. The system released 52% of metronidazole in 10 h, indicating a sustained drug release. In view of this, it is possible to conclude that the liquid-can crystalline system based on plant raw material (ucuuba butter) can be used as promoting drug sustained release, as alternative to conventional products. The authors thank CNPq and UFOPA for financial support.

Poly(pseudo)rotaxanes as promising formulations for antifungal drug delivery to the vaginal

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Background: Poly(pseudo)rotaxanes (PPR) are supramolecular gels formed by the combination of amphiphilic molecules and cyclodextrins (CD). Our group has recently demonstrated the ability of two small pegylated surfactants (Gelucire® and Kolliphor®) to form these systems with CD and to solubilize terbinafine (TB). PPR hold several advantages for topical applications, such as a thixotropic behavior that attains good spreadability and residence time and an improved drug bioavailability due to higher drug loading and CD permeation enhancer properties. Still, to our knowledge, these systems have not yet been evaluated for vaginal drug delivery. Objective: To evaluate PPR potential for antifungal delivery to the vaginal mucosa. Methods: PPR containing TB 2% were obtained using Kolliphor® RH40, Gelucire® 48/16, and different α-CD concentrations (5 and 10%). Simple and mixed PPR were fully characterized. Safety was evaluated using HET-CAM test. Formulation's performance was assessed in a vertical permeation model developed by our group, which uses entire porcine vaginas ex vivo. Conventional permeation experiments with excised vaginal tissue were performed as control. Antifungal activity attainment of final formulations was evaluated against Candida albicans and C. glabrata cultures. Results: All formulations were non-irritant according to HET-CAM test. PPR with 10% αCD showed superior mucoadhesion compared to the other formulations (p<0.05). Conventional horizontal permeation studies could not differentiate formulations (p>0.05). However, PPR presented a better performance in vertical ex vivo studies, achieving higher drug penetration in the vaginal mucosa (p<0.05), which is probably related to the prolonged residence time of the formulation. In addition, the antifungal activity of TB in the formulations was maintained. Conclusions: The better performance in a more realistic model evidenced the remarkable potential of PPR for vaginal drug delivery. Hence, when the formulation is challenged by gravity, PPR resist and promote higher drug penetration than other formulations. More importantly, formulation's viscosity and drug delivery control had no negative impact on the antifungal activity.

Microparticles based on pectin and retrodegraded starch containing pomegranate peel extract for antimicrobial use against Staphylococcus aureus

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Zoonotic bacteria such as the *Staphylococcus* species infect animals and humans, causing various illnesses, including infections in the gastrointestinal tract (GIT), and methylcycline-resistant *S. aureus* is one of the most dangerous pathogens for animal and human health. In this work, microparticles (MPs) based on pectin and retrograded starch were prepared to guarantee the release of phytocompounds present in the pomegranate peel extract (PPE) in order to obtain antimicrobial activity against *S. aureus* in GIT. After quantifying the total phenol content (TPC) and total antioxidant activity (TAA) of the dry extract of PPE obtained in ethanol, the MPs were prepared by the ionotropic gelation method using aluminum chloride as a crosslinking agent. The formation of MPs was confirmed by scanning electron microscopy (SEM) and the mean diameter was determined by Leica MZ APO® stereoscope. The swelling index (SI%) and erosion index (EI%) were performed using hydrochloric acid (HCl; pH 1.2) to mimic the stomach, and phosphate buffer saline (PBS; pH 6.8 and 7.4) to mimic intestinal conditions. The antimicrobial activity against *S. aureus* (ATCC 25923) was investigated in solutions containing the MPs in PBS at 8.25, 16.5, 25, and 33.5 mg.mL-1. Gentamicin and MPs without extract in PBS at the same concentrations were used as a positive and negative control, respectively. Finally, the hemolysis index (HI%) for the solutions microparticles in PBS was determined by UV-VIS spectrophotometry at 540 nm. TPC value in the dry extract was 60.54 mg.GAE.g-1 and the % reduction of DPPH was 90.11% when compared to a solution of gallic acid prepared at the same concentration (50 mg.mL-1). The formation of MPs was confirmed by SEM and it was observed that the MPs had a regular spherical shape. The particle's mean diameter was 1269.72 (± 254.97) µm. The values of SI were 414, 116, and 92% at pH 1.2, 6.8, and 7.4, respectively; EI% values were 42, 31, and 36. MPs preserved the extract's antimicrobial activity against *S. aureus*: was observed growth inhibition from the solutions of MPs prepared in PBS between 16.5 and 33.5 mg.mL-1. HI% values for these solutions showed that MPs were classified as slightly hemolytic. These results could be useful for developing dosage forms for treating GIT infections caused by *S. aureus* and should be further investigated in vivo models. The incorporation efficiency of PPE in the MPs will be studied.

Microencapsulation of Arthrospira sp. LEB-18 biomass for enteric controlled release: Proof-of-Concept

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Background: Microalgae-derived proteins are novel drug candidates whose use is limited due to general instability and loss of activity upon oral administration. Microencapsulation by spray drying has emerged as an alternative technique to improve long-term storage stability and gastrointestinal stability. Objectives: We sought to prepare spray-dried microparticles containing microalgal biomass to improve protein preservation and stability during oral administration. Methods: *Arthrospira* sp. LEB-18 biomass was selected as microalgae model due to its pharmacological effects. Eudragit L100 (EL100) was selected as the wall material for pH-dependent release in the gut microenvironment. Later, isoleucine was added as an anti-sticking agent for the drying process. Microparticles were prepared according to 22 factorial design (n=3). The protein content of the samples was determined after resuspension in phosphate buffer and the entrapment efficiency (EE) was estimated by the ratio between the detected protein and the expected protein. Characterization was also performed by Fourier-transformed infrared spectroscopy (FTIR), X-ray diffraction (XRD), and scanning electron microscopy (SEM). Results: All samples could be resuspended in aqueous solution after shaking. The highest measured EE was 31.44 ± 2.75% (p < 0.05). The FTIR spectra showed no changes compared to the starting materials. The XRD patterns show the characteristics of a semi-crystalline material for all samples, although the observed patterns are different when comparing the raw materials and the microparticles. SEM images showed microparticles, however EL100 does not appear to cover the entire microalgal surface. Conclusions: Spray-drying does not seem to negatively affect the chemical properties of the microalgae biomass. Digestibility tests using simulated gastric fluid followed by SDS-PAGE electrophoresis are currently underway to confirm the previous results and to verify protein stability on the microparticles. These results may indicate that EL100 is suitable for encapsulating the biomass of *Arthrospira* sp.

In vivo wound healing and in vitro antimicrobial activity of carbomer gel containing pomegranate peel extract at 2.5% w/w

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Bioactive compounds from medicinal plants are suitable candidates for use as substitutes for synthetic active pharmaceutical ingredients (APIs). In this work, a gel based on dry crude pomegranate peel extract (DCPPE) was prepared for use as antimicrobial and wound healing. The DCPPE was incorporated into a carbomer gel at a concentration of 2.5% w/w, and samples were kept under refrigeration (UR) and room temperature (RT) for 90 days. The total phenols content (TPC) in the gel DCPPE-based was investigated using Folin-Ciocalteu method. The in vitro antimicrobial efficacy of gels kept under both conditions for 30 days was evaluated against Gram-positive and Gram-negative strains by the disc-diffusion method. Tetracycline discs were used as a positive control and pure gel (with and without preservatives) as a negative control. The gel DCPPE-based was used in the treatment of excisional lesions in rats by topical application (500 mg) daily for a period of 21 days. Gel base and silver sulfadiazine (SAg) ointment at 1% w/w were employed as negative and positive controls. Progressive changes in the wound area were assessed planimetrically by photographic image collection, and the epithelialization rates were determined. In gel DCPPE-based maintained at UR and RT for 30 days, the reduction in TPC was less than 10%. The existence of an inhibition zone was observed for the positive controls and the absence of it for the negative controls, confirming the accordance with CSLI protocol. There was inhibition of growth against strains of *Staphylococcus aureus*, *S. epidermidis*, *Escherichia coli*, and *Pseudomonas aeruginosa* for the gels stored under both conditions. There was progressive closure of the lesions over time, with no necrosis or secretion, except in the animals treated with the SAg ointment, whose lesions presented a moist appearance indicative of maceration, and absence of hair in the center. There was no significant difference (p < 0.05) between ulcer healing rates and the closure of the wound area after 21 days, with values close to 1 and 90%, respectively. However, it was possible to observe in the histopathological analysis the occurrence of greater re-epithelialization in the groups of animals treated with pure gel and in the gel DCPPE-based. From the analysis of the results, it is possible to conclude that the gel DCPPE-based can be considered an alternative to commercially medicines containing synthetic APIs for the intended use.

Custom-made support for iontophoresis application in teeth: proof-ofconcept evaluation of antimicrobials delivery for endodontic treatment

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Background: Current endodontic treatment aims to disinfect the root canal system based on biomechanical preparation associated with root canal irrigation, microbial control, and obturation of root canal system. Due to the complex anatomy of the root canals, endodontic treatment presents many chances of reinfection. Iontophoresis, a technique that applies a mild electric current to promote drug penetration in biological tissues, could be used to improve the penetration and distribution of antimicrobial drugs used in endodontic treatment, reaching inaccessible areas of root canals. For this, it is crucial to have an in vitro model employing excided teeth to evaluate proper iontophoretic parameters. Objective: This work aims to fabricate and evaluate a custom-made support for the iontophoresis application in teeth and verify the viability of such an approach. Methodology: A 3D printed system was designed and developed for dental iontophoresis using Ag/AgCl electrodes. Teeth will be treated with staining solutions, sliced, and visually analyzed for drug distribution within root canal structures. Two antimicrobial molecules were chosen for proof-of-concept experiments based on their in vitro activity against Enterococcus faecalis (ATCC 29212) and their resistance to electrical current. Results: The custom-made support was successfully printed and could hold the teeth. The inner part of the support was filled with buffer solution enabling the positioning of the return electrode. Iontophoretic current was successfully applied. Chlorhexidine and Domiphen Bromide resist the electrical current through UV spectrum analysis before and after iontophoresis. MIC test demonstrated that 4,88µg/mL of Chlorhexidine and Domiphen Bromide are the minimum inhibitory concentration compared to 410,2µg/mL of positive control. Hence, these drugs will be used in further experiments. Conclusions: A custom-made support for the iontophoresis application in teeth was successfully developed. In vitro application of iontophoresis in excised teeth seems to be a practical approach for establishing the better parameters for a future iontophoretic endodontic treatment. Further studies employing antimicrobial agents must be performed.

Development and characterization of a scaffold for three-dimensional lung tissue cell culture

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Three-dimensional cell cultures are used to screen new compounds and to study host-pathogen interaction. The aim of this work is to standardize and characterize a platform for lung cell culture. To form the scaffold, fish gelatin and brown seaweed alginate (3% w/v) were dissolved in water and 350µl of 2-hydroxyethyl methacrylate (7% v/v), 25µl of ammonium persulfate (10% w/v), 5µl of N,N,N,N-tetramethylethylenediamine,125µl of polyethylene glycol, and 25µl of glutaraldehyde (25% v/v) were added. After 12 h of reaction at -15 °C, the scaffold was dried inside a 10 mL-syringe and cut into 0.5 cm slices. Scaffold stability was tested after incubation in PBS (35°C) and weekly weighing. In the swelling kinetics, the scaffold was immersed in water and weighed every 30 seconds to obtain the percentage of water uptake. The scaffold was stained with calcofluor white and hematoxylin-eosin after preparation by histological techniques for observation in microscope. Rheological analyzes were performed to assess elasticity with frequency sweep and tests flow analysis. The cytotoxicity was performed on lung epithelial cells A549 by the resazurin method and in *Aspergillus fumigatus* by the CFU count, after immersion in 0.1M glycine. The scaffold lost 20-35% of the initial mass in the first week, but in the following weeks there was no reduction. After 1 minute, in water, the hydrophilic scaffold swelled rapidly. The scaffold formed large pores and a typical lung tissue arrangement, mimicking the extracellular matrix and the rheological parameters showed very elastic scaffolds with a high level of interaction between their compounds. No cytotoxicity was observed on lung cells and *A. fumigatus*. In summary, the scaffold is stable, has high water swelling and elasticity, has large pores, and is a non-toxic platform for eukaryotic cells. Then, these data will allow the use of the scaffold for the development of a complex three-dimensional structure that mimics lung tissue.

4-Methoxy Chalcone: An inhibitor of Cathepsin-K and its osteogenic activity in biodegradable scaffolds in bone regeneration therapy

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Background: For bone remodeling the grafts must have specific characteristics, such as being osteoconductive, rigid, osteoinductive, safe, absence of size restrictions, long duration and reasonable cost. The 4-methoxy chalcone (4-MC) is a very promising compound with osteogenic, anti-inflammatory and Catepsin-K inhibitor action. Objective: The aim of this work was to evaluate a scaffold of biodegradable polymer containing 4-MC. Methods: Microparticles (MPs) of PLGA 7507 containing 10% of 4-MC were used to prepare scaffolds by sintering process. The MPs and scaffolds were characterized by scanning electron microscopy, particle size diffraction, encapsulation efficiency, thermal behavior and drug release by Franz cells. Bone regeneration was evaluated in the critical sized defect in calvarial bone model, where the control (white scaffolds) and treated groups were euthanized after 30 and 60 days and the caps removed for transillumination analysis, histological analysis and SEM. The Catepsin-K inhibition activity was analyzed by molecular docking. Results: The scaffolds showed pore size of 100 - 200 µm and drug release of 70.45% in 60 days, both desirable parameters in bone tissue therapy. The scaffolds containing 4-MC demonstrated a wound closure of approximately 26% and 63% for the control and 30-day treated groups, respectively and 59 and 79% for the control and 60-day treated groups, respectively. A large amount of cells and blood vessels were found within the pores of the scaffolds, especially in scaffolds with 4-MC. The presence of 4-MC allowed greater formation of collagen and primary and secondary bones compared to the control group. Molecular docking studies evidenced the cathepsin-K inhibitory action of 4-MC. Therefore, this activity can be considered the basis of the mechanism by which chalcone promotes bone regeneration. Conclusions: The developed platform is an effective system for bone regeneration therapy.

Development of lipid systems for potential improvement of the biopharmaceutical properties of drugs

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Background: Many bioactive molecules have low solubility in aqueous fluids, resulting in low bioavailability and difficulty in absorption. There is an urgent need for new formulations to optimize biopharmaceutical properties without the need to synthesize new derivatives. Nanostructured lipid systems - such as nanoemulsion (NE) and microemulsion (ME) - are nanocarriers that can lead to an increase in the apparent solubility of bioactives. Objective: Therefore, the aim of this work was to develop lipid nanocarriers and evaluate their physicochemical properties and stability. Methods: The emulsified systems containing surfactants, water and oil were developed with the help of a phase diagram using sonication technique. From this diagram, two formulations (F1 and F2) were reproduced and characterized by transmission electron microscopy (TEM), dynamic light scattering (DLS), zeta potential (ZP) and polydispersity index (PdI). Stability was analyzed in the oven (≈ 28 ºC) and in the refrigerator (6 to 8 ºC) over a period of 90 days, measuring in particular the average of the parameters conductivity, pH, and turbidity. Results: Physicochemical characterization revealed that F1 exhibited spherical structures and nanometric diameters (112.14 nm ± 1.19), ZP (-11.5 mV ± 1.09), and PdI (0.25 ± 0.01). F2, on the contrary, showed misshapen structures and nanometric diameters (55.38 nm ± 0.40), ZP (-9.10 mV ± 1.56), and PdI (0.55 ± 0.00). In terms of stability, F1 achieved conductivity (84.20 ± 8.33 µS/cm) and pH (5.80 ± 0.22), and F2 achieved conductivity (158.20 ± 9.94 µS/cm) and pH (6.20 ± 0.30). The samples were macroscopically fluid and homogeneous, but F1 had high turbidity (990 ± 11 NTU) and F2 had low turbidity (175 ± 21 NTU). Both formulations stored in the refrigerator remained stable, with F1 characterized as NE, with a higher average droplet size, but with a lower PdI, possibly representing a more stable system and suggesting that it may improve the biopharmaceutical properties of drugs, and it would be an interesting object of study for subsequent incorporation of a drug and evaluation of its pharmacological activity. F2, on the contrary, is characterized as an optically transparent systems such as ME and liquid crystals, which have a smaller droplet size. Conclusion: The malformed structures are likely the cause of the increase in PdI value. Therefore, a more detailed physicochemical characterization might be required, e.g., by small-angle X-ray scattering.

Corona CAD detector as an alternative for drug substances without cromophores: the case of Paromomycin Sulfate topical formulation

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Background: Paromomycin (PA) is a broad-spectrum aminoglycoside antibiotic and has recently been used to treat visceral and cutaneous leishmaniasis. Recently Farmanguinhos, a Brazilian public pharmaceutic laboratory, started the development of a new pharmaceutical formulation for topical use to reduce the side effects of paromomycin. However, the development of an analytical method for assay and related substances for this drug can be challenging because it is a non-chromophore compound, without a UV/vis-absorbing structure. Objective: Develop and validate a stability-indicating method (SIM) for the assay and impurities of PA with sensibility to detect substance without chromophores. Method: In order to improve the sensibility to detect substance without chromophores, liquid chromatography system with Corona® Charged Aerosol Detector (CAD), a universal detector, was used since it charged substance with a neutral and ionized gas. Several parameters were evaluated using the cyanic column (CC), such as changing work PA concentration, solvent concentration, pH, flow rate, oven temperature and vaporization temperature (VT). Placebo, pharmaceutical active ingredient and the formulation were subjected to acid, alkaline, oxidative and thermal degradation (50°C) due to evaluate the selectivity. Result: The chromatography conditions developed include a CC (250 x 4,6; 5µ) maintained at 25°C and a MF of 10 mM ammonium acetate –acetonitrile (70:30,v/v) at a flow rate of 0,5mL/min, VT 60°C. PA´s impurities were well separated from the main peak, indicating a good selectivity; during method validation the relative standard deviation (RSD) was 1.0% for the same sample, indicating high repeatability. The linearity obtained was approved with correlation coefficient (R) of 0.992. Intermediate precision was approved by presenting the RSD under 3.0%. The limit quantitation has been proved to 0.4µg/ml. Robustness test showed that the flow rate, vaporization temperature and extraction time must be strictly followed. Conclusion: In conclusion, the successful HPLC-CAD method development allowed the stability and release analyses of a new pharmaceutical form. Our group acknowledge BNDES for the financial support.

Electro-stimulated melatonin-loaded silk fibroin films for wound healing

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Background: Wound repair is one of the most complex biological processes in the human body. Therefore, a dressing that works at various stages of the healing process is desirable. Films based on silk fibroin, a natural polymer with good hemostatic properties, low inflammatory potential, and permeability to oxygen and water vapor, are an exciting proposal to serve as a platform for a dressing. Incorporated melatonin, a drug with anti-inflammatory and immunomodulatory effects, can sustain its release, allowing its action in defined stages of healing. External stimuli can also be applied to the dressing, making it possible to modulate this process. It is known, for example, that low-intensity electrical current affects cell migration and aids in wound healing. Objective: to develop electric conductive fibroin-based films added with melatonin and evaluate the influence of iontophoresis on drug release. Methods: The mechanical and structural properties of the films were evaluated using techniques such as scanning electron microscopy, atomic force microscopy, infrared (ATR-FTIR), X-ray, and contact angle. The release profile was determined by applying iontophoresis at 0.2 mA/cm² for 30 min. Melatonin was quantified using HPLC-PDA. Results: The incorporation of melatonin into the films did not change the tensile strength, but increased the elongation from 22.5% to 38%, reduced the roughness from 64 nm to 10 nm, and increased the crystallinity from 0.264 to 0.297. ATR-FTIR analysis showed the presence of amide groups characteristic of beta-sheet motifs. Melatonin incorporation did not significantly change the contact angle of the film with water. However, it increased with formamide from 19 ± 2 to 36 ±1 °, decreasing the surface free energy of the film by 1.2 times in this solvent. The surface free energy of the melatonin-loaded film, of approximately 60 mN/m, was similar in hydrophilic and lipophilic media. The film showed electrical current conductive properties, but iontophoresis did not influence the release of melatonin, which was sustained for up to 96 h. Conclusions: The sustained melatonin release, combined with the film's flexibility, tensile strength, balanced hydro/lipophilic surface properties, and conductive properties, suggests its potential application as an electrically stimulating dressing

Amphotericin B degradation in medium-chain triglyceride solution

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Background: Despite the known degradation reactions affecting the antifungal Amphotericin B in aqueous media, it is still unclear if phenomena such as oxidation, adsorption or photodegradation are the main pathways of AmB degradation in lipid-based media Aim: The purpose of this work was to determine the degradation pathway of Amphotericin B (AmB) and its kinetics in lipid-based solutions. Methods: Mixtures of AmB in lipophilic solvent media were stored under different conditions, such as surface area, temperature, light exposure, presence of antioxidants and other co-solutes. AmB was quantified by HPLC and UV-Vis spectrometry. Empirical models were proposed, and degradation rate constants were estimated by nonlinear regression. Results: The HPLC method was precise and accurate with linearity from 4.45 to 52.0 nM. Surface area studies revealed that adsorption to glass did not affect AmB loss. Unsaturated oils and methanol better preserved AmB compared to medium chain-triglyceride. Temperature increased AmB loss in a nonlinear behavior and the presence of antioxidants reduced its degradation. Under dark conditions, autoxidation was the predominant degradation pathway of AmB in oil, which undergoes a complex degradation. Under light exposure, photo-oxidation accounted for AmB loss, which appeared to be of pseudo-first order. Conclusion: AmB oily samples should be preferably stored in glass vials protected from light with the addition of antioxidants. Furthermore, this work encourages further investigation in other media for future complex modeling and estimation of AmB degradation and kinetics in lipid-based formulations.

Keywords: Anti-infective, Chemical stability, Oxidation

Synthesis of conjugated polylactides with carbohydrate-based ligands for cell targeting

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Introduction: Surface-decorated nanoparticles (NP) for drug delivery represent an innovation in the nanomedicine field and warranty of reliable active vectorization of drugs. The presence of targeting molecules on the NP surface allows their specific interaction with receptors present on the target cell membrane, promoting cellular uptake through ligand-receptor interaction. The conjugation is carried out by covalent attachment of polymer with the ligand. Carbohydrates-based ligands have been widely studied due to the expression of lectin receptors in different cell types and in dysfunctional cells. Objective: The present work aims to synthesize polymers conjugated with ligand derived from carbohydrates for biological targeting that will be used in carbohydrate-decorated nanoparticles. Methodology: Alkyne functionalized polylactide (BCN-PLA) was synthesized by an organocatalyzed opening-cycle polymerization reaction, using an alcohol functionalized cyclooctyne derivative as initiator and specific catalytic conditions. The conjugation of BCN-PLA with the azide functionalized carbohydrates was carried out by a strain promoted 1,3-dipolar cycloaddition reaction. The polymers were characterized by gel permeation chromatography, 1H nuclear magnetic resonance (1H NMR) and diffusion-ordered (DOSY) spectroscopy. NP were prepared by the nanoprecipitation method and characterized in terms of average size, polydispersity index (PdI) and zeta potential. Results: BCN-PLA had a number average molecular weight (Mn) of 4,400 g/mol with chemical structure confirmed by 1H NMR analyzes. The 1H NMR signals of the polymer and the carbohydrate showed the same diffusion coefficient in DOSY analysis, indicating that both belong to the same molecule, confirming the covalent attachment of the carbohydrate to the polymer. Decorated-NP had an average size of 171 nm, with narrow size distribution (PdI<0.3) and a zeta potential of -39,6 mV. Conclusion: The synthetic methodology used allowed obtaining a carbohydrate-conjugated polymer successfully used for the preparation of stable carbohydrate-decorated NP.

Effect of protein particle morphology and salt on the stabilization of amylopectin and xyloglucan water-in-water emulsions

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Water-in-water (w/w) emulsions arise from the thermodynamic incompatibility between polymers in solution and present low interfacial tension values. This class of emulsions can not be stabilized through the addition of amphiphilic molecules like surfactants, since the interface between the two aqueous phases is broad. An alternative for stabilizing these emulsions is the addition of solid particles that adsorb at the w/w interface through the so-called Pickering effect. In the present work, the main objective was to stabilize amylopectin and xyloglucan emulsions using protein particles with different morphologies. As emulsion stabilizing agents, β-lactoglobulin nanoparticles with spherical shape (microgels) or with a higher aspect ratio (nanofibrils) were synthesized through protein heating at 80 °C and 90 °C, at pH 6.9 and 2.0, respectively. The stability of w/w emulsions was assessed macroscopically and by confocal laser scanning microscopy (CLSM) images. The emulsions were evaluated at pH values ranging from 4.0 to 7.0 and at different salt conditions. Both particles were able to stabilize the w/w emulsions – the microgels adsorbed at the interface of the droplets at pH < 5.0 and gelled the continuous phase when the pH > 5.0, whilst the nanofibrils presented Pickering effect at higher values of pH. Through the addition of different saline concentrations, the effect of screening the repulsive potentials led to protein particle flocculation at the interface, which made the emulsions stable for longer periods of time. Although there is still much to be studied and discussed, the present work presents itself as a step towards the development of food products that are nutritious, dietetic, and stable.

Polymeric cellulose acetate films containing a spiro-acridinic derivative

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Introduction: Advances in science have led to the development of new controlled drug delivery systems (NDDSs) that can be presented in the form of polymeric films. These demonstrate several advantages such as providing good adhesion to the skin, local action with prolonged drug release and optimization of therapeutic effects. Thus, the use of AMTAC06 (drug synthesized by a research group from UEPB) associated with cellulose acetate (AC) for the development of formulations is an example of (NDDSs) that represents an alternative to the traditional healing treatment, as it is of low cost, biodegradable and has fluid absorption capacity. Objective: The objective of this work was to develop a spiro-acridine-derived cellulose acetate (AMTAC-CAF) film. Methods: Cellulose acetate films were prepared by the solvent evaporation technique with AMTAC06 dispersion in the polymer matrix. They were characterized by measuring the degree of swelling (DS), bending strength test (BRT), Fourier transform infrared spectroscopy (FTIR) and X-ray diffraction. Results: The DS showed an increase in the maximum mass of AMTAC-CAF of 212.12% and the drug-free films (CAF) showed a value of 120.17%. AMTAC-CAF maintained its integrity up to an average of 315 curves, while CAF showed resistance to an average of 282 curves. FTIR data demonstrated specific bands for cellulose acetate and AMTAC. CAF and AMTAC-CAF maintained the FTIR profile of the CA, only with a decrease in intensity. The AMTAC-CAF diffractogram showed a decrease in crystallinity when compared to the isolated drug powder and the appearance of two crystalline reflections at 8.04° and 17.98°. Conclusion: Therefore, the incorporation of AMTAC06 in the AC matrix sought an increase in the degree of flexural strength and an increase in the flexural strength capacity. The FTIR showed the disappearance of peaks referring to the drug in the AMTAC-CAF, indicating that it was incorporated, which was also evidenced in the profile found in the XRD. Given the physicochemical characteristics of the new product, the evaluation of the healing potential in skin wounds can be envisaged as a future perspective.

Liquid crystalline systems for curcumin delivery

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Background: Curcumin (CC) is obtained from Curcuma longa L. and presents several biological activities such as anti-inflammatory, antitumor, antimicrobial and antioxidant. It´s a lipophilic molecule with poor oral bioavailability. Liquid crystalline systems (LCS) of monoolein (MO) can be interesting vehicles to deliver CC due to their amphiphilic nature. The presence of additives can modulate drug release and improve LCS´properties. Objectives: to study LCS-containing additives (oleic acid-OA associated or not to propylene glycol-PG) for CC delivery. Methods: LCS of MO/water (70:30) with CC (0.1%) and additives OA (1.0-10.0%) and PG (5.0-15.0%) were evaluated. Systems were prepared by mixing the oily phase (MO/OA/CC) and the aqueous phase (water/PG) at 40°C. Mesophases were identified after 24 hours by polarizing light microscopy. In vitro drug release studies were performed in a dissolutor at 37°C and 50 rpm agitation for 6 hours. The amount of CC released was quantified spectrophotometrically at 425nm. Results: The system with no additive presented cubic phase, as expected, and released 50.3% of CC after 6 hours. The addition of OA (1.0%) reduced drug release (36.7%) and maintained the cubic phase. An increase in OA content (5.0-10.0%) promoted hexagonal phase with drug releasess of 33.0 and 34.3%, respectively. Lipophilic additives generally induce phase transitions to hexagonal phases in MO/water systems. Association of OA/PG (5.0/10.0%) induced cubic phase, even in the presence of the lipophilic additive and drug release of 37.0%. PG is a solubilizing additive and may increase drug partition to water channels. LCS with higher PG content dissolved during the assay and was discarded. Drug delivery from LCS can be affected by the mesophases presented and their internal structure or by interactions between drugs, MO, and additives. Our results suggest that reduced release from LCS-containing additives should be related to the increase of their lipidic domain, retarding the release of lipophilic CC. Conclusions: Additives affected mesophase formation and drug release reducing CC delivery in both cubic and hexagonal phases, probably due to lipophilic interactions. LCS presented the potential to deliver CC for several routes.

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Controlled release system of tamoxifen from the clay mineral montmorillonite

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Tamoxifen (TMX) is a drug used in the treatment of breast cancer. Studies focusing on new release systems from clay mineral montmorillonite (VHS) have been carried out. Thus, the aim of this study was to verify the influence of obtaining nanostructured hybrid system (NHS) TMX/VHS on in vitro release. The NHS were prepared from a solution of TMX 1660 mg.L-1 with 0.1 g of VHS at different pH values, 3.0 (VHS/TMX/pH3), 4,0 (VHS/TMX/pH4) and 5,0 (VHS/TMX/pH5), and the solid fraction obtained by centrifugation. The dissolution of the TMX and NHS was performed in simulated medium pH 1.2 and 6.8, containing 100 mL of buffer, maintained at 37 ± 0.5 °C and shaken at 100 rpm. The samples were centrifuged, diluted and quantified by HPLC, equipped with a diode array detector. Furthermore, the systems were characterized, after dissolution, by XRD, FTIR, TGA/DTG and DSC. It was found that the in vitro release process of the drug is not influenced for the preparation of NHS, but by the interaction between the drug and the clay surface. A relatively low amount of TMX is released at pH 1.2 for all NHS, indicating a strong interaction between TMX and VHS, due to the characteristics of the molecule, of the medium and the ionic species present. However, for the NHS VHS/TMX/pH5 around 40% of the TMX is released in 48 hours in pH 6.8 medium, because it has less affinity with the clay surface than the other NHS formed. The losses of the crystalline reflections by the XRD demonstrated the release of the TMX to the medium and the formation of a non-crystalline phase by leachin, as well as formation of a more hydrophilic surface without additional interactions with the VHS surface. Therefore, the mechanism of interaction is inversely proportional to release by controlling drug release to the medium, could be a promising material as a pharmaceutical excipient for anticancer drugs.

Poly(pseudo)rotaxanes with Eugenia uniflora dry extract for onychomycosis treatment

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Background: Fungal nail infections, also known as onychomycosis, is usually treated by oral antifungal therapies. However, they have often been related to different side effects. Therefore, topical application is preferable and considered an unmet clinical need since those formulations should overcome the restrictions imposed by nail structure and adhere to the nail surface with adequate viscosity to remain at the application site. Objective: Formulations using mixed micelles associated with α-cyclodextrin (αCD) containing a high concentration of Eugenia uniflora (EU) dry extract were developed to improve gallic acid (GA), ellagic acid (EA), and myricitrin (MYR) permeation through the nail and proximal nail fold (skin) aiming onychomycosis treatment. Method: Mixed polymeric micelles (Polymer 1 and 2) were prepared, and αCD was added to that dispersion to form poly(pseudo)rotaxanes (PPR). Formulations were characterized in terms of particle size, morphology by transmission electron microscopy (TEM), rheological behavior, drug release, nail and skin permeation, and interaction with the nail plate. Results: formulations obtained with the dry extract had a micelle mean size of around 30 nm, confirmed by the TEM images. The rheological behavior showed that the αCD addition directly influences the viscosity, thixotropic, and solid-like viscoelastic properties. Besides, release studies showed that the higher the viscosity, the greater the controlled release of the analyzed compounds, notably for MYR. TEM demonstrated that αCD significantly changed hooves morphology. Also, permeation studies demonstrated that αCD increased the permeation of chemical markers, increasing the permeation to deeper regions of the nail plate or skin layers. Conclusion: The presence of αCD in the formulation affects their aspect, performance, interaction with the nail plate, and AG, AE, and MYR release. Rheology, membrane interaction, and permeation enhancement indicate that PPR is probably a potential alternative to the delivery of antifungal agents from the EU dry extract to treat onychomycosis.

Obtaining hybrid ph and thermosponsive systems based on polaxamine 1304 and laponite as potential drug carriers

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The study aims to evaluate the phase behavior of hybrid systems formed by copolymers in branched stellar blocks of poly ethylene oxide and poly propylene oxide (PEO-PPO) chains, the Tetronics (TET). TET 1304 was analyzed, with about 21 PEO units and 27 PPO units, with EHL between 12-18 (manufactured by BASF Corporation) and a synthetic nanoclay, Laponite RD (LAP, manufactured by BYK Additives & Instruments), rheology modifier , under the influence of pH and temperature (TEMP), optimizing the performance of 10–100 nm nanopolymer micelle systems in different pharmaceutical applications and drug delivery systems. The TET solutions were submitted to magnetic stirring in concentrations ranging from 1 to 20% (m/m), in ambient TEMP for 20 min/1200 rpm; then, the LAP (1.5 and 3% w/w) was inserted and stirring was maintained for 72h. TET dilutions were prepared to obtain concentrations of 1%, 5%, 10%, 15% and 20%. Aliquots were taken to obtain different pH values (pH 2.0;4.5;5.5 and 7.4). The behavior was evaluated as a function of TEMP and pH, using a dry bath from 25ºC to 80ºC, classifying the samples. The formation of gels at various TEMP and concentrations was observed, making it possible to highlight systems with the phase transition close to the body TEMP. As a result, we have the TET1304+1.5%LAP systems at pH 5.5, 4.5 and natural pH; TET1304+3% LAP at pH 5.5 and 4.5. The 10% and 1% systems at pH 4.5 stand out with both clay concentrations. This would be relevant for some formulations with the characteristic of being in liquid form at room temperature and taking the form of a gel at body temperature; Applications can range from topical vaginal gels, rectal enemas, after-sun lotions and treatments, mouthwash for lesions and aphthous stomatitis, eye lubricants and sexual lubricants combined with a spermicide. Therefore, these were also subjected to rheological studies. It is necessary to continue characterizing these systems and building diagrams that guide these applications in pharmaceutical and controlled-release formulations.

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Anodic iontophoresis as a tool of bacterial growth control

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Microbial contamination is a crucial factor that delays the wound healing process. Electrical stimulation has been explored as a non-pharmacological alternative method to wound healing and may be a promising approach to inhibiting bacterial contamination. The electrical stimulation can be performed by iontophoresis, a non-invasive procedure that uses a constant low-intensity electrical current, whose main application is to increase skin drug penetration. The literature lacks a systematic study that evaluates the electric circuit parameters and the structural differences in the bacteria wall, which can directly influence the antimicrobial effect. This study investigates the antibacterial effect of anodic iontophoresis in a gram-positive, *Staphylococcus epidermidis*, and a gram-negative, *Escherichia coli*, strain. In vitro experiments were performed in bacterial cell suspension using Ag/AgCl electrodes and saline bridges to apply anodic iontophoresis in an electrical circuit mounted in series. After 24h of the current application, the antibacterial effect was evaluated by counting colony-forming units by the drop-plate method. Different times of electric current's application (15, 30, and 60 min) and intensities (0.2, 1, and 5 mA) were analyzed for bacterial viability by performing a 3^2 factorial design. The results showed that the electric current's intensity and application time directly influenced the viability of *E. coli*; the greater the intensity and time of iontophoresis application, the greater its antimicrobial effect. Otherwise, only the application of the highest current intensity for 60 min in *S. epidermidis* showed a significant difference from the control. Therefore, anodic iontophoresis was a powerful tool against the gram-negative bacteria studied, being a promising strategy to treat infected wounds.

Electro-stimulating emollient films based on hyaluronic acid loaded with acetyl hexapeptide-3 for the skin aging treatment

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Skin aging leads to a decrease in collagen, elastin, hyaluronic acid (HA), aquaporins, and lipids proliferation, resulting in a tissue with a rough appearance, expression lines, and wrinkles, with compromised barrier function and susceptible to oxidative stress and cellular oxidation. The acetyl hexapeptide-3 (Hex-3), an inhibitor of acetylcholine at the neuromuscular junction, has been applied topically to replace botulin toxin injections. It is claimed to reduce muscle contraction, diminishing fine lines and wrinkles. Electrical stimulation is another strategy used in skin aging treatments. It stimulates cell proliferation and regeneration and, thus, improves the skin's appearance. This work aims to develop emollient polymeric films containing Hex-3 and evaluate the electric current influence on the film's components' release. Films based on silk fibroin, chitosan, and HA were developed and added with nanostructured lipid carriers as a source of lipids for the skin. Bi-laminated films containing Ag/AgCl electrodes were prepared. They were characterized mechanically and morphologically. Hex-3 release from the film was studied in the presence and absence of a constant electrical current (iontophoresis) of 0.2 mA for 15 min. The release of a structural film component, HA, was also evaluated by spectrofluorimetry after using HA conjugated to FITC in film preparation. In vitro studies in fibroblast (3T3) and keratinocyte (HaCat) cultures were conducted to assess the films and iontophoresis cytotoxicity. The Hex-3 influence on the gene expression of the antioxidant enzyme SOD2 was evaluated by qPCR. The films presented a homogeneous surface, with some irregularity characteristic of the presence of nanoparticles, without pores. The atomic force microscopy showed that the films are viscoelastic and rough. About 2% of HA was released from the films in contact with PBS for 30 min. The Hex-3 release rate was iontophoresis independent, with constant kinetics of 2%/h for up to 12 h. Films and electrical current were not cytotoxic to fibroblast and keratinocytes under the conditions studied. Hex-3 caused an increase in SOD2 expression, suggesting its potential to protect the skin against oxidative stress. Iontophoresis influence on the HA and Hex-3 skin penetration will be further evaluated, as the Hex-3 effect on acetylcholine activity. Acknowledgements: CAPES and iNanocare.

Development and characterization of lipid platforms for transdermal administration of leflunomide

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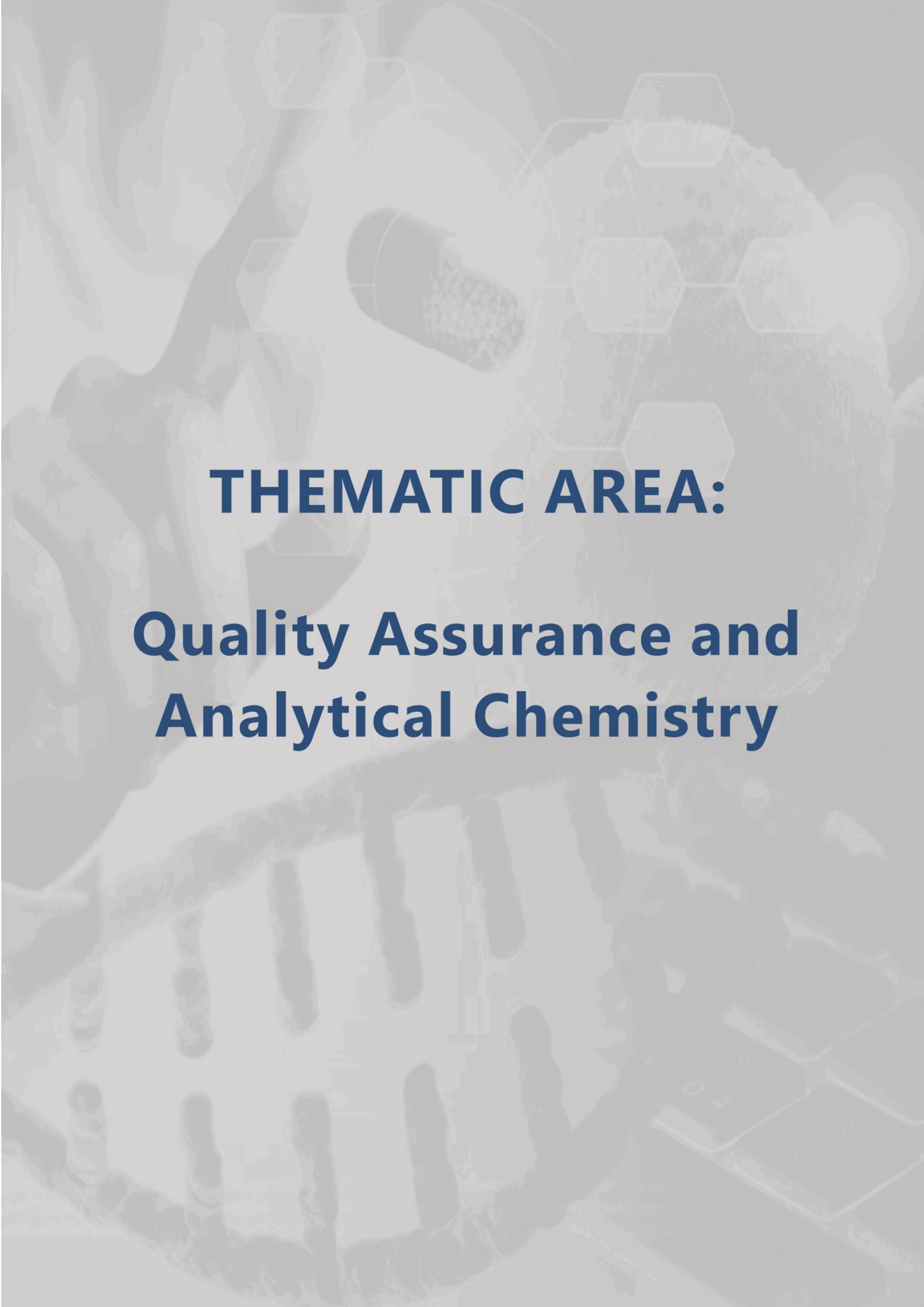
Background: Leflunomide is an immunomodulatory agent indicated for the treatment of rheumatoid arthritis. However, this systemic administration is associated with several adverse effects. The transdermal application of Leflunomide in nanosystems proves to be a technological alternative to minimize adverse effects. Objective: To develop and in vitro characterization of nanostructured lipid carriers to cutaneous delivery of Leflunomide. Methods: The present study initially evaluated two different methods of preparation of nanostructured lipid carriers (NLC) containing leflunomide. The emulsification-diffusion method by solvent displacement was compared with the method of fusion emulsification. The average particle size and polydispersity index (PDI) of NLC were utilized as preliminary parameters to evaluate the influence of the preparation method. Pseudo-ternary phase diagrams were constructed using different combinations of mass proportion of lipids, surfactant and co-surfactants for the optimization of the formulation. A stability study was carried out to evaluate physicochemical parameters for a period of one month at different temperatures, and using a Turbiscan® Lab evaluated the kinetic stability. Results: From the studies of pre-formulation were select the excipients of the formulation. In the emulsification method, it was possible to form nanoparticles, but not with the appropriate characteristics. The fusion emulsification method presented the formation of nanoparticles with 245 nm and PDI of 0,456 however, did not show stability. Therefore, from the pseudo ternary phase diagrams and using the fusion emulsification method it was possible to obtain a formulation with particle sizes between 200 – 300 nm and PDI smaller than 0,300. Furthermore, the stability studies showed no significant loss in the mean size and size distribution after 1 month. The results obtained with the Turbiscan® lab verified that the optimized formulation did show kinetic stability in the availed period. Conclusion: It was possible to obtain NLC with physicochemical characteristics and stability adequate for topical delivery of leflunomide, we expect to evaluate the influence of the incorporation of Leflunomide on the aspects of the systems obtained through the phases diagrams, to evaluate the parameters of drug load, encapsulation efficiency and the in vitro characterization of release and skin permeation of nanoparticles to an improvement in the delivery of Leflunomide.



THEMATIC AREA:

Quality Assurance and Analytical Chemistry

Validation of a chromatographic method for determination of Resveratrol in skin samples

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Introduction: Resveratrol (RES), a polyphenol found in edible fruits and plants, mainly in the leaves, the pericarp of berries, and grape seeds, is known for its anti-inflammatory, antioxidant, antiviral, neuroprotective, and anti-aging properties. However, RES low hydro solubility (Log P = 3.10), instability in the presence of UV light, and low skin permeation demand the development of novel drug delivery systems to enable its use in dermatology. Objective: The present study proposes to develop and validate a chromatographic method to quantify RES in skin samples to support the evaluation of its cutaneous absorption. Methodology: An analytical method by High-Performance Liquid Chromatography (HPLC) was developed using a mobile phase consisting of phosphoric acid 0.1%/acetonitrile (70:30, v/v), which flowed at 0.8 mL/min in a C 18 reversed-phase column used as stationary phase. The oven was kept at 30 ºC, and UV detection of RES was set at 310 nm. The validation parameters analyzed were selectivity against skin samples, linearity, precision, accuracy, and limits of detection and quantification, according to the guidelines of ICH Q2B (1996). Results: The chromatographic analysis following the developed method showed a RES retention time at 8.8 min. Chromatographic method was selective and linear in a concentration range of 1.0 – 20.0 µg/mL (linear correlation coefficient = 0.998). The method was also precise, with a variation coefficient of less than 3%, meeting the acceptance criteria of ICH. The limits of detection and quantification were, respectively, 0.07 µg/mL and 0.21 µg/mL. The recovery rate of RES from the skin samples (following drug extraction with methanol under stirring for 24 h) were 91.5%, 80.5%, and 73.8% from the stratum corneum, follicular casts, and remaining skin, respectively. Conclusion: The chromatographic method was straightforward and suitable for RES quantification in skin samples. It may be a valuable tool in developing dermatological formulations containing the natural drug. Acknowledgements: FAPDF (Grant #00193-00000721/2021-04, Project 41/2021) and CAPES.

Characteristics of voluntary reports of adverse events about the Baricitinib approved to act against Covid-19

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Introduction: Since 2020, when the Covid-19 pandemic was declared, studies have been underway to obtain drugs that can prevent and treat the disease caused by Sars-Cov-2. Baracitinib had its indication approved in September 2021 in Brazil for treating Covid-19 in adult hospitalized patients who require non-invasive oxygen. It is a selective and reversible inhibitor of janus kinase enzymes, which act in hematopoiesis, inflammation, and immune function. Objective: To characterize the reports of adverse drug events (ADE) baracitinib in the pandemic of COVID-19. Method: This is a descriptive, quantitative study, which used public data from Anvisa's Pharmacovigilance Panel, available on the Agency's website, on notifications from 09/17/2021 to 07/10/2022. Results: 40 reports were registered in VigiMed in the analyzed period, but it was not possible to establish whether the ADE were due to use for Covid-19 or rheumatoid arthritis, for which it was already approved. Of these, 28 (70%) reports were sent by consumers or other non-health professionals, and 11 (27.5%) by medical professionals. All were forwarded to Anvisa by the manufacturing company. As for the characteristics of the patients, 90% (n=36) were female and 52.5% (n=21) were older than 45 years. It is noteworthy that 15 reports did not inform the patient's age. In the 40 notifications 60 ADE were reported, 66.6% (n=40) of which were considered by the notifier as severe, 20 with clinically significant effect, 17 hospitalizations or prolonged hospitalization, 1 life-threatening and 5 deaths. The notifier did not inform the outcome (whether recovered or not) in 58.3% (n=35) reports. The notifier was not aware of the classification of product indication and adverse event. One is the reason for use, the other the consequence of use, respectively. Given the available data and the inconsistency regarding the classification of adverse events by the public data panel, it was not possible to assess the causality of ADE. Conclusion: Recognized as a science, Pharmacovigilance of products approved by Anvisa is fundamental to monitor the effects of drugs on the Brazilian population. However, to evaluate the ADE of baricitinib in use for Covid-19, it is necessary to qualify the reports, which should be done by the company before sending the information to the Brazilian Agency. Training and dissemination actions on the importance of report are essential.

Development of pyrimethamine suspensions and stability assessment

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Background: Pyrimethamine (PYM) is an antagonist of the folic acid rote used to treat congenital toxoplasmosis. However, there is no available an oral liquid pharmaceutical form suitable to the pediatric patients in Brazil. An alternative to provide it is to prepare oral suspensions from the crushed tablets (Daraprim® 25mg) to meet these patients demands. Objective: The goal of this work was to develop and evaluate the stability of a PYM suspension in extemporaneous formulations in order to obtain stable formulations appropriate for pediatric use. Methods: Suspensions containing 2 mg/mL PYM were prepared from the powder of the crushed tablets. Two different concentrations of the polymer were used in the suspensions: carboxymethylcellulose 0.5% (F1) and carboxymethylcellulose 0.75% (F2). Methylparaben was used as preservative, pH was adjusted if necessary to 7.0 ± 0.5 and the volume was made up with distilled water. The particle size, pH, viscosity and PYM assay were evaluated just after the preparation (day 0) and after 30 days. The suspensions were assayed by a method previously developed and validated by our group. Results: At zero time the results for F1 and F2 were, respectively: pH 7.10 ± 0.18 and 7.28 ± 0.05; particle size were 94.20 ± 2.12 µm and 110.50 ± 4.95 µm; percentual assay were 88.0 ± 5.3% and 97.3 ± 1.8% of the label claimed. After 30 days the results of F1 and F2 were, respectively: pH 7.22 ± 0.18 and 7.25 ± 0.12; particle size 111.50 ± 10.62 µm and 119.00 ± 4.24 µm; assay values were 88.1 ± 6.4% and 91.2 ± 1.4%. No changes in the viscosity were observed during the period. The low PYM content in F1 and the dispersion between the individual assays were attributed to the fluctuation, caused by the low particle wettability. Concerning F2, a decrease in the PYM level was observed, but the mean value met the pharmacopeial requirement for oral suspension (90.0 – 110.0%, USP 2016), and the low RSD values indicated the dose homogeneity. Conclusions: The set of preliminary results indicated that F2 is a promising formulation to provide PYM as oral suspension to treat congenital toxoplasmosis.

Development and validation of an uplc method to assay pyrimethamine and methylparaben in oral suspensions

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Background: Pyrimethamine (PYM) is an aminopyrimidine used in the treatment of congenital toxoplasmosis in neonates and children; however, the drug is available only as tablets. Therefore, our research group developed oral suspensions to circumvent this limitation. Objective: Considering the advantages of the chromatographic techniques and the low specificity of the pharmacopeial UV method for the developed products, the objective of this study was to develop and validate a stability indicating UPLC method to assay PYM and methylparaben (MP) in the suspensions developed. Methods: The method employed a chromatographic system equipped with PDA detector; the mobile phase was composed by solution A (0.05M sodium acetate buffer pH 4.5) and solution B (acetonitrile:methanol, 70:30 v/v), in a proportion of 60:40 (v/v), flow rate of 0.2 mL/min, detection at 272 nm and RP-C18 column. The linearity was studied in the concentration range of 0.5 to 25 µg/mL. The accuracy was carried out by the recovery 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 the robustness was evaluated by making deliberated changes in some chosen factors (pH, flow rate and mobile phase proportion). Results: The optimized conditions resulted in a chromatographic run of 6 minutes, wherein the PYM and MP retention times were 4.1 and 4.9 minutes, respectively. The method was linear in the range of 0.5–25 µg/mL, with linear regression and absence of deviation from linearity. The mean recovery was 99.70% (n=9) and the RSD values in the precision study were < 2%, which met the requirements. In all stress test conditions, the PYM and MP peaks did not suffer interference, which proved that the method was specific. The suspension excipients also did not interfere with the PYM and MP peaks. The robustness assessment showed that the small alteration of the factors did not affect the results. Conclusion: A simple and fast UPLC method was developed to determine PYM and MP in oral suspension; it is also appropriate to be used in stability studies.

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Validation of a chromatographic analytical method for Nile Red quantification in skin samples

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Introduction: Fluorescent markers are often used to investigate the skin penetration mechanism of nanostructures developed for topical application. These molecules allow capturing images for primarily qualitative analysis of the deposition of nanoparticles in specific skin structures, such as hair follicles. However, accurate quantitative analysis of such transport also needs to be explored. Objective: This work aimed to develop and validate a chromatographic analytical method for quantification of Nile Red (NR) extracted from skin samples. Methodology: NR was quantitatively analyzed by HPLC with fluorescence detection. A C18 column (150×4.6 mm, 5 µm) was used as the stationary phase. The mobile phase consisted of methanol-water at a ratio of 93:07 (v/v), which flowed at 1.0 mL/min. The injection volume was 10µL, and the column oven was kept at 30◦C. The following validation parameters were analyzed: selectivity, linearity, precision, accuracy, and limits of detection and quantification, according to the guideline of ICH Q2B (1996). Results: The selectivity was determined by NR quantification in the presence of biological matrices. There was no significant difference between the contaminated and uncontaminated samples in peak areas and retention time. The method was linear in a concentration range from 0.5 to 7.5 µg/mL (r2=0.9993). Precision was measured as 2.1%, within the acceptance criteria (< 5%). The accuracy was evaluated by means of NR recovery from the skin samples, in which the extraction was carried out using methanol as a solvent, under mild agitation for 24 h. The percentages of NR recovered were 80.7% from the stratum corneum, 104.7% from the follicular casts, and 98.4% from the remaining skin. Finally, the limits of detection and quantification were 0.4 and 1.1 µg/mL. Conclusion: The validated method was considered adequate for quantifying NR in skin samples, allowing the quantitative investigation of new nanoformulations' effect on drug deposition in the skin layers.

Method development and validation for quantification of alpha phelandrene

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Background: Alpha phelandrene (α-PHE) is a cyclic monoterpene with suggested anti-inflammatory activity that is present in several essential oils. The development and validation of a suitable analytical method for the analysis is important for quality control processes of formulations containing this active. Validation ensures, through experimental studies, that an analytical method is reliable and meets the requirements of analytical applications. Objective: The objective of this work is to develop and validate a method for quantifying α-PHE. Methods: The analytical method development and validation were performed in a Shimadzu high performance liquid chromatograph (HPLC) (LC20AD) coupled to a photodiode array detector (DAD) (SPD-20A). A Supelco C18 Discovery HPLC reversed-phase column (150 mm × 4.6 mm, 5 µm) was used as the stationary phase. The DAD was set to scan the samples from 200 nm to 900 nm and the fixed wavelength 263 nm, the maximum absorption wavelength in the UV spectrum for α-PHE. The analytical method will then be validated according to the guidelines of the International Conference on Harmonization. Results: The method was initially developed in an isocratic system according to the literature. After the initial parameters, were tested different mobile phase proportions, flows, injection volumes and oven temperatures. Getting optimal parameters with an injection volume of 10 µL, oven temperature at 45°C and a gradient system, 0-12 minutes 85:15 (ACN:H2O) 12-22 minutes 100:00 (ACN:H2O) 22-40 minutes 85:15 (ACN:H2O) at a flow rate of 0.5 mL/min. Then, an equidistant ethanolic α-PHE analytical curve (5.00 – 30.00 µg/mL) was injected. The analytical curves resulted in a correlation coefficient (r) of 0.9997, which meets the requirements (>0.990). The linear regression equation for the α-PHE calibration curve was y=182269x−1285.6. The high numerical value of the angular coefficient (182269) indicated an adequate response of the method to changes in concentration. Conclusion: The developed method is suitable for validation, having its linearity approved. It is currently being tested for specificity, selectivity, linearity, precision, accuracy, robustness, quantification, and detection limits.

Application of Analytical Quality by Design in Stability Indicating Method Development for Pharmaceutical Products

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Background: Stability indicating methods (SIM) are essential for pharmaceutical industry by supporting drug development and quality control activities. Usually, SIM development is challenging due to the complexity of the chromatographic separations involved. As an alternative for the traditional development approach (one factor at time), risk based enhanced analytical quality by design (AQbD) approach offers an in-depth method understanding by using the design of experiments (DoE) as a key component, since a high number of parameters can be improved with minimum experimental trials. Objective: To develop a SIM by High Performance Liquid Cromatography (HPLC) for the stability study of ritonavir (RTV) tablet using AQbD approach. Method: AQbD was applied by Analytical Target Profile definition, risk parameter identification and risk assessment to develop a SIM. Placket- Burman screening design (PB) was done to evaluate the HPLC conditions affecting the responses, followed by central composite design (CCD) to determinate a response surface. Results: From the Ishikawa diagram, eight critical parameters of the method were identified and tested in a DoE. The PB assessment, identified the most relevant analytical conditions affecting the chromatographic, leading to the development of a SIM for the determination of RTV and its degradation products. The HPLC method use a Kinetex C18 column (100mm x 4.6mm, 2.6µm) maintained at 50°C, gradient elution mode with 0.5mL/min flow rate and detection at 254nm, mobile phase A was composed of a 15mM ammonium acetate buffer pH 5.7 and mobile phase B was composed of a mixture of acetonitrile and water. The method's robustness was tested by applying a CCD that gave rise to a design space and mathematical models that explain the effects of variables on critical analytical responses. The critical method risk parameters were mitigated by the elaboration of the control strategy from the application of the Hazard Analysis and Critical Control Point risk analysis tool. Conclusion: The developed and validated SIM can be used as an analytical tool for quality control and stability studies of RTV formulations. Our group acknowledge FINEP for the financial support of our work.

Validation of a chromatographic method for simultaneous determination of minoxidil and betamethasone in skin samples

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Introduction: Alopecia areata is an inflammatory, autoimmune disease that causes hair loss. Common treatments are not curative. Indeed, topical corticosteroids (like betamethasone) only counter the autoimmune causes of the disease, and in persistent cases, an association with minoxidil can also be indicated. However, developing such topical formulations demands an analytical challenge, i.e., quantifying both drugs extracted from such a complex matrix as the skin. Objective: To validate a chromatographic method to quantify minoxidil and betamethasone in skin samples. Methodology: The chromatographic method was developed using a gradient mobile phase consisting of phosphoric acid 0.1%/acetonitrile (90:10,v/v) at the time 0-2 min; (80:20) at 2-6 min; (70:30) at 6-13 min; (30:70) at 13-20 min; (20:80) at 20-30 min; and (90:10) at 30-35 min, which flowed at 1.2 mL/min in a C18 column used as stationary phase. The oven was kept at 40 ºC, and UV detection of minoxidil and betamethasone was set at 285 nm e 240 nm, respectively. The validation parameters analyzed were selectivity against skin samples, linearity, precision, accuracy, and limits of detection and quantification, according to the guideline of ICH (Q2B, 1996). Results: The method showed a minoxidil and betamethasone elution at 5.5 min and 19.3 min, respectively. It was selective against skin samples and linear in a concentration range of 0.5 – 15.0 µg/mL (linear correlation coefficients>0.993). The method was also precise, with a variation coefficient of less than 2.8%. The limits of detection and quantification were, respectively, 0.21 µg/mL and 0.63 µg/mL for minoxidil, and 0.04 µg/mL and 0.13 µg/mL for betamethasone. The recovery rate of minoxidil from the skin samples (following drug extraction with 5 mL methanol for 24 h) was 96.40 ± 0.08%, 99.52 ± 0.02%, and 97.92 ± 0.04% for stratum corneum, follicular casts, and remaining skin, respectively. Betamethasone was recovered at 98.86 ± 0.08%, 97.66 ± 0.02% and 97.16 ± 0.10%. Conclusion: The chromatographic method was straightforward for simultaneous minoxidil and betamethasone quantification in skin samples, which will benefit the development of novel topical formulations to treat alopecia areata.

Design of Experiments: challenges and overcoming in stability indicative method development of pediatric Isoniazid + Rifampicin formulation

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Background: Rifampicin (RIF) and Isoniazid (INH) are first line agents for the treatment of tuberculosis (TB), usually in fixed-dose combination (FDC) tablets or capsules. However, FDC available in Brazil are not suitable for kids. The FDC INH + RIF (50+75) mg dispersive tablets emerge as a good alternative to pediatric TB treatment. Since it is a new dosage form, it is mandatory to develop a stability indicative method (SIM), a quantitative analytical method for sample stability analysis, validated, capable to measure with accuracy the active pharmaceutical ingredient (API) content, degradation products and other compounds of interest without interference. Objectives: The aim of this work was to develop and validate a robust and fast SIM by high efficient liquid chromatography (HPLC) to these drugs and their impurities using design of experiments (DOE) tools. A major challenge is the very different physicochemical properties of the API and the low stability of RIF and its degradation products. Methods: Methods described in literature for INH and RIF were compiled and the most promising were evaluated. Starting from a base method were realized two separated DoE for INH, RIF and their respective impurities. Results: Through the DoE, it was possible to evaluate the factors that most impact the responses obtained, making it possible to optimize the methods and obtain excellent chromatographic parameters. Posteriorly the two methods were aggregated and optimized in a single method that can quantify all this compounds. A forced degradation study also was performed with the drugs to evaluate unknown impurities. Conclusion: DoE is an excellent tool to obtain a fast and robust stability indicating method that meets all specified chromatographic parameters.

Hen's Egg Test on Chorioallantoic Membrane Method as an alternative method for evaluating irritation potential of plant preparations

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Background: The safety assessment of substances before entering the market is required and in vivo tests were developed, including the Draize eye test that uses albino rabbits for the ocular irritation assessment. However, this assay is highly criticized for causing animal suffering. An alternative method that is receiving increasing attention is the Hen's Egg Test on Chorioallantoic Membrane (HET-CAM), that is able to categorize the irritancy potential of substances based on the observation of vascular response of coagulation, lysis, vasoconstriction, and hemorrhage. The matrix complexity of plant preparations may have impact on the experimental design, therefore, the HET-CAM assay may need to be adapted and validated to categorize plant preparations. Objective: To map the applicability of the HET-CAM assay in assessing the irritation potential of plant preparations and their technological derivatives, such as cosmetic and topical formulations. Methods: Original papers published were searched in three databases - Embase, PubMed, and Web of Science - without any restriction as to language and date of publication using terms HET-CAM, plants, and irritation, combined with Boolean operator "AND". The search excluded isolated compounds from vegetal origin. Results: The total number of articles retrieved was 142, but after excluding duplicates and applying selection criteria, 18 original papers were eligible, being the first study published in 2007. Considering the vegetal species tested, 6 out of 24 belong to the Lamiaceae family. Essential oils were the most common natural products evaluated by HET-CAM and showed to cause more severe irritation than the aqueous extracts. Most publications were from Brazil, followed by Austria, which is in line with the banning of animal testing for cosmetics. Expressive methodological differences were found, even among the major published guidelines. Conclusions: although the interchangeability between the irritation values obtained by the HET-CAM assay is restricted and conditioned to the methodology applied, the use of HET-CAM is encouraged as a screening assay prioritizing the reduction of animal suffering until its validation is ensured by regulatory agencies. Authors thank CAPES/PROEX.

Quality by design as a tool for optimizing dissolution tests for tablets containing Glyburide, marketed in Salvador, Bahia, Brazil

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Glyburide is a hypoglycemic drug, belonging to the sulfonylurea class, used in the treatment of type 2 diabetes mellitus (DM). The use of tools for test optimization and dissolution profiles, evaluation of dissolution efficiency (ED) and pharmaceutical equivalence (EF) are important to provide information about the prediction of its bioavailability. This work aims to propose new conditions, through experimental design and response surface, for the test and dissolution profiles of tablets containing Glyburide (generic, similar and reference) and to obtain data about ED and EF in these products. The factorial design of 24 was applied, studying the variables time, pH, volume and rotation per minute (rpm), to establish optimal dissolution conditions using spectrophotometry in the ultraviolet region, at 230 nm. The Pareto chart identified significance in all variables, as well as in the interactions between them. Subsequently, the optimization was performed using the Doehlert matrix as a response surface methodology, obtaining the optimal experimental conditions: pH 7.2; 75 rpm; 500 ml and 60 min. The dissolution profiles of the tablets (generic, similar and reference) were traced, the DE and the f1 and f2 factors were calculated. The analyzed pharmaceutical specialties showed comparable dissolution, ED and EF profiles. The new conditions for the dissolution test proposed in this work contribute and strengthen the area of drug quality control in the country, as well as expand the application of Quality by design studies in pharmaceutical practice.

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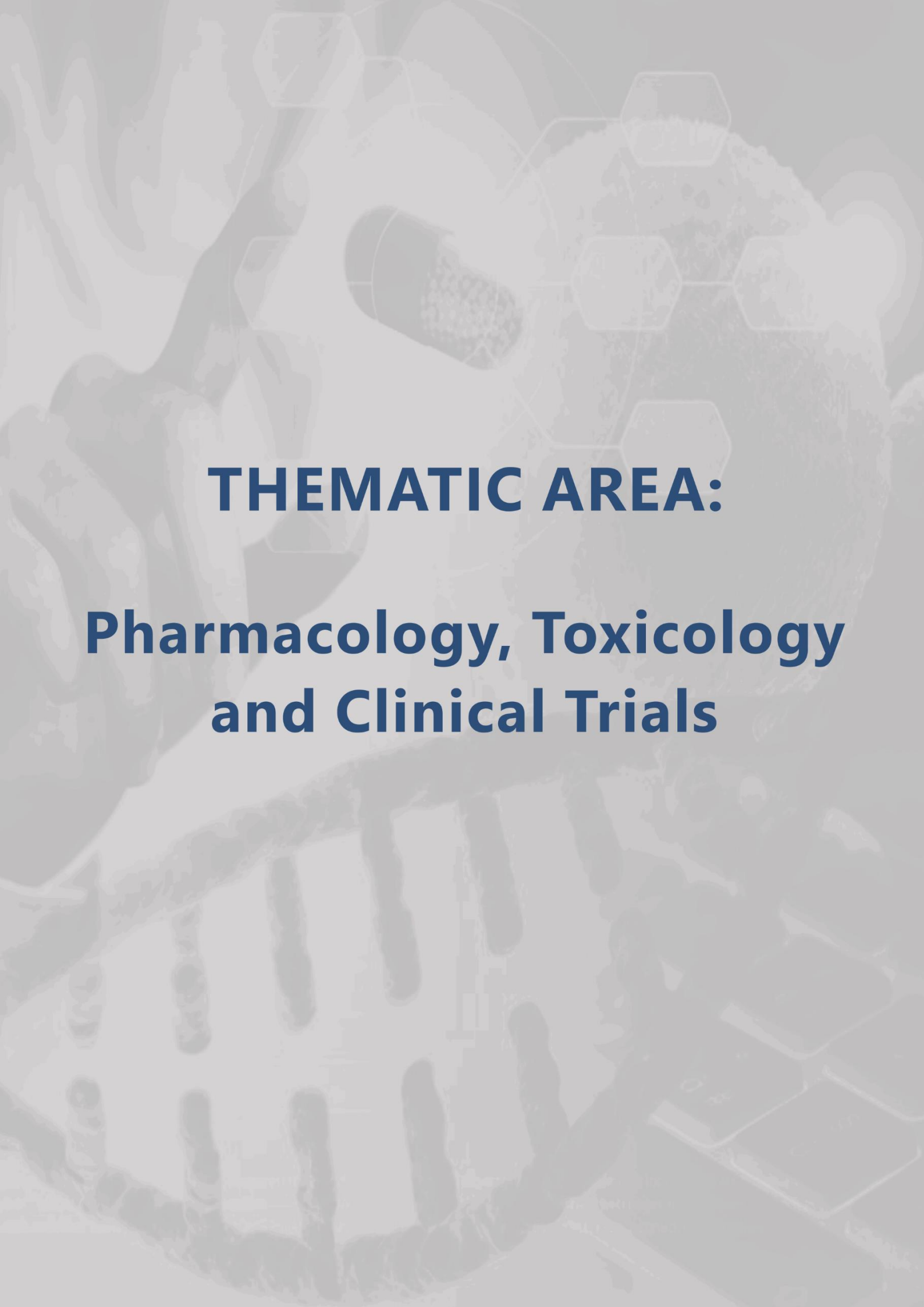

THEMATIC AREA:

Pharmacology, Toxicology and Clinical Trials

Evaluation of the effects of Metformin on glial cells activation in a Diabetic Encephalopathy model

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Background. Diabetes mellitus (DM) has been a major public health problem worldwide and it is associated with diabetic encephalopathy, which is caused by changes in the central nervous system. Neuronal dysfunctions are related to the activation of nuclear factor kappa beta (NF-κB), which is involved in neurodegenerative and inflammatory processes. The NF-κB pathway may be inhibited by the activation of AMP-Activated Kinase (AMPK), and its pathway may be activated by metformin. Objectives. This study aimed to evaluate the effects of metformin on the activation of glial cells in an experimental diabetes model. Methods. For this purpose, 42 Swiss male mice aged 10-12 weeks, were divided into: Control, Streptozotocin (STZ), STZ + Metformin 100 mg/kg (MET 100) and STZ + Metformin 200 mg/kg (MET 200) groups. Mice with glycemia ≥270 dl/mL were considered diabetic, treatments were started and, after 8 weeks of treatment, the animals were anesthetized and euthanized. The Barnes Maze test for memory and learning assessment was started the week before euthanasia. The animals' brains were processed in order to perform immunohistochemistry (IHC) tests with the anti-Iba-1 and anti-GFAP antibodies. For the Western blotting, hemispheres of the animals were homogenized for the quantification of AMPK.Results. After evaluation by the Barnes test, memory deficit was identified in the STZ group and also an increase in spatial memory after treatment with 200mg/kg of metformin when compared to the STZ group. The IHQ of the GFAP showed there was an increase in the expression of the marker, evidencing an astrocytic activation in the STZ group. Treatment with 200 mg/kg metformin was able to reverse that in diabetic animals. In the evaluation of AMPK by Blotting, treatment with metformin was able to increase its expression when compared to STZ animals, which showed a significant reduction in the quantification of this marker. Conclusion. The results showed that neurological changes, such as cognitive deficit and reactive gliosis, had an impact on memory formation during diabetes, and metformin was shown to be a potential neuroprotective. Metformin, besides having antihyperglycemic function, can be considered an important agent in the treatment of neurodegenerative diseases and neuropathies.

A biomarker prospection of exosomal microRNAs for metastatic prostate cancer.

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Background: Prostate cancer (PC) is the fourth most common type of cancer in the world and the most recurrent among men in all regions of Brazil, second only to non-melanoma skin cancer. Despite presenting high cure rates, advanced PC has a high risk of mortality due to the few treatment alternatives for metastatic disease, which indicates the importance of predicting the risk of metastasis through non-invasive biomarkers. Recently, exosomes have been described as having an important role in the communication between tumor cells and the tumor microenvironment and the content of exosomal microRNAs (miRNAs) are potential biomarkers of the disease. Objectives: To isolate and characterize exosomes derived from metastatic prostate cancer (mPC) cell lines (LNCaP and PC-3) and to evaluate the expression of miRNAs, compared with the healthy prostate line RWPE-1. Methods: The isolation of exosomes was performed by serial ultracentrifugation followed by identification by transmission electron microscopy and nanoparticle tracking analysis. MiRNA signatures in exosomes and cells were evaluated by microarray analysis and expression was validated using RT-qPCR, and further bioinformatics analysis. Results: The samples showed spherical vesicles from 40 to 200 nm in diameter with cup-shaped morphology, characteristic of exosomes. The total RNA obtained was analysed by the microarray technique and fourteen miRNAs were identified as candidates for specific non-invasive biomarkers. The expression of five miRNAs was validated, which confirmed that miR-205-5p, miR-125b-5p, miR-148a-3p, miR-183-5p, and miR-425-5p were differentially expressed in cells as well as in exosomes. Bioinformatics analysis showed that miR-425-5p is associated with residual tumor, T and N pathological stages, and TP53 status in PC samples. Analysis of the gene ontology of negatively correlated and predicted targeted genes showed enrichment of genes related to bone development pathways. The LinkedOmics database indicated that the potential target HSPB8 has a significant negative correlation with miR-425-5p. Conclusions: In conclusion, this study reveals differences in miRNA expression profiles between tumor and non-tumor samples, indicating that such miRNAs are potential biomarkers for mPC.

Characterization of the microbiota of donor milk supplemented with the mother's own milk, administered to premature newborns

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Background: Breast milk is considered the ideal food for newborns, and it is known that preterm newborns are especially in need of the components of their own mother's milk, as they present numerous signs of immaturity of organs. However, in many preterm births, the mother is unable to produce an adequate amount of milk or even any amount at all. In these cases, donor milk becomes the best option. This milk goes through the pasteurization process for microbiological safety; however, it is known that this process also causes depletion of bioactive compounds in milk. Studies have shown that it is possible to restore potentially beneficial naturally occurring microorganisms in donor milk by inoculating 10% of the mother's milk and incubating this milk at 37°C for a period of 4 hours. The present project establishes the hypothesis that inoculation of the mother's own milk with pasteurized donor milk results in the partial restoration of the milk microbiota. Objective: To determine the differences in the composition and diversity of the microbiota of donor milk supplemented with mother's milk, administered to newborns with less than 32 weeks of gestational age. Methods: The microbiome analysis of 8 newborns' mother own milk (LM), 8 donors' milk (LP) and the mix of those two (supplemented milk - Li) is performed by sequencing the V3 and V4 regions of the 16S portion of the ribosomal RNA, (Illumina MiSeq), followed by bioinformatics and statistical analysis. Results: The bacterial composition of the samples at the phylum level was observed, with a predominance of the *Firmicutes* and *Proteobacteria* phyla in the three types of milk, and a small increase of *Actinobacteria* and *Bacteroidetes* in the LM and Li groups was observed, with no statistical differences. Conclusions: Although no statistical difference was found, considering the immature microbiota of the premature baby, a qualitative difference in milk composition should already make a difference for its modulation, especially with the increase of natural bacteria in human milk such as *Actinobacteria* and *Bacteroidetes* in personalized milk.

Metabolomic identification of possible biomarkers and metabolic pathways correlated with Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative disease that is diagnosed mainly through clinical symptoms. Therefore, it is essential to discover biomarkers that help in the diagnosis quickly and assertively. Metabolomics comprises the study of low molecular weight metabolites, through analytical platforms and statistical analysis, and can be used to determine biomarkers. Thus, the objective of this work was to evaluate, through metabolomic strategies, variations in the level of metabolites in the serum of patients with PD to identify biomarkers for diagnosis and regulated metabolic pathways. The blood of participants (control and PD patients) was analyzed using ultra-performance liquid chromatography coupled to a high-resolution mass spectrometer. The results were processed in MS-DIAL, analyzed in Metaboanalyst using univariate and multivariate statistical analyzes and dereplicated in MS-FINDER. Finally, an analysis of altered metabolic pathways was performed using the Metaboanalyst. Through the statistical analysis, a separation of the groups was observed and allowed the de-replication of 12 metabolites related to PD, out of a total of 3134 variables detected. From this set of metabolites, enrichment analyzes were performed to identify metabolic pathways, with 3 pathways being identified: metabolism of caffeine, arachidonic acid and primary bile acids. Therefore, the results allowed us to point out important information about possible PD biomarkers and metabolic mechanisms involved in the pathology as a support for the discovery of markers for diagnosis and therapeutic targets. Further studies are needed to establish the most promising metabolites for the development of diagnostic or therapeutic methods for PD.

Cytotoxicity of two natural sesquiterpene lactones against human melanoma cells

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Cutaneous melanoma is the greater malignancy skin tumor that can display one of the worse prognoses due to its high mortality rate and invasive metastatic characteristics. Despite breakthrough advances in therapeutic strategies, limitations and disadvantages have been reported to the currently available drugs. Natural products have been a rich source of medicines for millennia, and several evidences have demonstrated promising pharmacological activities of the extracts of Tithonia diversifolia from which tagitinins are purified, especially attributed to tagitinin C (TC). Thus, the objective of this work was to check the in vitro cytotoxic properties of TC and its isomer, tagitinin F (TF), against human melanoma cells. For the experimental development of this study, cell viability assays were performed using the MTT and trypan blue exclusion test; the cell migration was performed by scratch technique and cell cycle and type of cell death analysis were performed by flow cytometer. TC and TF inhibited the growth of melanoma cells in a concentration and time-dependent manner, and they presented a minor effect on normal skin fibroblasts. The cell migration was also suppressed in a time-dependent manner. The drugs induced apoptosis and TF promoted cell-cycle arrest in G2 phase. However, TC boosted the distribution of sub-G1 and showed higher cytotoxicity than TF. Both plant-derived sesquiterpene lactones showed a promissory anti-melanoma effect and our results suggest a tumor cell-selective killing activity. Future studies should be performed to assess the antitumoral response of TC and TF and how these natural products could negatively interfere on the complex oncogenic machinery.

Ibrutinib controls proliferation and induces apoptosis in metastatic melanoma cell line

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Background: The main clinical treatment strategies for melanomas comprise local resection, which tends to have a poor prognosis, as well as immune- and chemotherapy, which are limited by severe adverse reactions and limited efficacy. Recently, the use of tyrosine kinase inhibitors (TKI) has been evaluated as a therapeutic strategy for a number of tumors, including hematological and solid cancers. Objective: Here, we evaluated the anticancer potential of the TKI Ibrutinib in melanoma cells of the MEWO metastatic cell line. Methods: Mewo cells were treated with Ibrutinib for 48h and the cytotoxic effect of the TKI was determined by MTT. Using the IC25 and IC50 concentrations, we evaluated by flow cytometry whether Ibrutinib was able to control the proliferation and induce apoptosis of Mewo. Finally, we evaluated by spectrophotometry the levels of LDH released by Mewo after treatment with ibrutinib and whether this TKI could compromise the mitochondrial membrane potential of this cell line. Results: After 48h of treatment, the MTT test revealed that 8.3 and 12.3 µM of Ibrutinib reduced the viability of MeWo by 25 and 50%, respectively. We then confirmed that the treatment of the MeWo cell line with ibrutinib induced apoptosis of these cells (p=0.006) and efficiently reduced cell proliferation (p<0.0001). In line with the cytotoxicity tests, the treatment of MeWo with Ibrutinib induced a greater LDH release, compared to non-treated cells (p=0.0001). Interestingly, the mitochondrial membrane potential of the MeWo lineage was not altered by treatment with Ibrutinib, which indicates that the observed cell death process may not involve the intrinsic pathway of apoptosis. Conclusion: Although preliminary, the results obtained in this study show that ibrutinib exerts an anticancer effect against an aggressive melanoma cell line. Additional experiments are needed so that we can molecularly characterize the mechanisms involved in the observed cellular processes.
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Influence of the quorum sensing molecule produced by pseudomonas aeruginosa on the functional properties of mesenchymal stem cells

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Pseudomonas aeruginosa is an opportunistic pathogen whose virulence and host interaction mechanism are composed of quorum sensing (QS) dependent cell density. Mesenchymal stem cells (MSCs) have been explored to treat a variety of clinical conditions, especially immune disorders. Several studies have shown that the initiation of MS with INF increases the immunomodulatory property of these cells. In this study, we investigated the influence of QS N-(3oxododecanoyl) (3oxododecanoyl) on the biological properties of MSC-indifferent or not to INF-γ priming. Using the MTT test, we demonstrated that, after 24h of cell use, OdDHL (10 and 50μM) compromised the viability of MSCs, regardless of INF-γ priming. , we observed that OdDHL (10 and 50μM) induces apoptosis in MSCs and this effect seems to be more pronounced in MSCs licensed with INF-γ. MSC effects increase when treated with ODHL50μM and greater release of the enzyme lactate dehydrogenase (LDH) in the extracellular medium, which was potentiated by priming cells with INF-. In non-toxic 0.5 and μM cells, we observed that ODHL increased the migratory potential of MSCs, especially in licensed cells. However, OdDHL doses also did not potentially affect MSC immunosuppressants. Furthermore, MSCs directly inhibit the growth of Pseudomonas aeruginosa. We demonstrated that licensing with INFγ increases the suppressive potential of MSCs, but not these cells from the deleterious effects protected by the high concentration of OdDHL. Although our study was developed in vitro, the findings indicate that lower doses can cause problems with cell viability, regardless of γ licensing.

Keywords: Pseudomonas aeruginosa, quorum sensing, OdDHL, Mesenchymal stem cells, licensing, antimicrobial peptides.

Galectin-9 expression in M1/M2 macrophages treated with conditioned medium from BxPC3 Pancreatic Ductal Adenocarcinoma cells

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Pancreatic ductal adenocarcinoma (PDAC) is characterized by a dense stroma envolved in therapeutic resistance. PDAC has a macrophage enriched tumor microenvironment (MT). Galectins are glycoproteins that modulate tumor behavior in PDAC and can be expressed in tumor-associated macrophages. Knowing that Gal-9 is expressed in cells potentially recruited by the MT, the aim of the study is to investigate Gal-9 in PDAC macrophage polarization. Macrophages were obtained from the differentiation of peripheral blood mononuclear cells (PBMC) by GM-CSF stimulus. After that, macrophages were treated with LPS + IFN-ɣ to induce M1 polarization and IL-4 + IL-13 for M2. Thus, those cells were treated with BxPC-3 conditioned medium for 48 hours. Gal-9 expression was evaluated by flow cytometry and immunofluorescence in macrophage subpopulations. After CD14+ CD11c+ cells selection, CD80 and CD206 markers were used for M1 and M2 immunophenotyping, respectively. Macrophages treated with BxPc-3 conditioned medium has polarized more to M2 phenotype than the M1. In addition, Gal-9 was shown to have higher expression in M2 macrophage than M1. In the control group (PBMC with GM-CSF); the intracellular labeling of Gal-9 was lower than M1 and M2. Immunofluorescence results confirmed the increase of the Gal-9 staining in M2 macrophages membrane in the presence of conditioned medium compared to M1. These results revealed that the soluble factors present in the BxPc-3 conditioned medium induces the M2 macrophages polarization and the increase in Gal-9 expression, which may be associated with the progression of PDAC. However, further studies are be need to investigate the Gal-9 role in tumor-associated macrophages activity and the greater immunosuppression by M2 than M1 macrophages treated in conditioned medium as well your utility as therapeutic target in PDAC.

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Assessment of serum levels of glycoprotein-130 in patients with PDAC

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Pancreatic ductal adenocarcinoma (PDAC) is characterized by its aggressive behavior, poor prognosis, resistance to chemotherapy being on of the tumours with the highest mortality rate in the world. An important feature of PDAC is its microenvironment, which plays an important and determinant role in tumor support. PDAC is formed by immune cells, nerve cells, fibroblasts, mast cells, soluble proteins, and an abundant extracellular matrix, building a unique microenvironment. These microenvironment components work together with neoplastic cells to promote tumorigenesis and progression. Among the molecules expressed, there is glycoprotein-130 that participates in IL6 signaling, initiating the intracellular signaling of some cascades. For this reason, the present study aimed to assess the levels of circulating gp130 in the serum of newly diagnosed patients with PDAC. Thus, peripheral blood samples were collected from 60 patients with a confirmed diagnosis of PDAC and from 60 healthy controls. The samples were processed to obtain the serum and analyzed by Elisa sandwich to analyze the levels of GP130. All statistical analyzes were performed using GraphPadPrism software (GraphPad Software Inc., San Diego, CA, USA) Student's t test was performed. The assessment of Gp130 levels showed a lower secretion in newly diagnosed patients with PDAC when compared to control subjects (p < 0.0001). The median of PDAC patients was 127.114pg/mL, whereas the median of the control group was 259.700 pg/mL. Within the PDAC group, when the levels of gp130 were correlated with the presence of the serum levels of CA19.9, there was no significant correlation p=0.8708. There was also no significant association with the presence of metastasis with p=0.7854 The results found until the moment allow us to state that our cohort has lower circulating levels of gp130 in patients with PDAC when compared to healthy individuals. More studies need to be done to correlate this.

Evaluation of galectins-1, -4, -12 serum levels in patients with liver and gallbladder cancer

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Background- Tumors that affect the liver and gallbladder have in common the absence of early symptoms and late diagnosis that contribute to high mortality rates. The galectin (Gals) family in humans suggests potential prognostic roles in several types of cancer, but their evaluation as markers in liver cancer and gallbladder cancer has not been described. Objectives- To assess serum levels of Gals-1, -4, -12 in patients diagnosed with liver cancer (HC) or gallbladder cancer (GBC). Methods- After approval by the ethics committee, serum samples were collected for the control group (n=92) and patients diagnosed with HC (n=19) or GBC (n=14) in the Hospital of Cancer in Pernambuco and Clinics Hospital of Pernambuco. The galectins were measured using the enzyme-linked immunosorbent assay for Gals-1, -4, -12, according to the manufacturer's instructions, and concentrations were determined by interpolation of the standard curve. Statistics were performed using the Mann-Withney test. Results- In the HC group, the male gender is predominated and the median age is 59 years (range 20-84). Patients included in the GBC group are mostly female with a median age of 69 years (range 41-80). Serum levels of Gal-4 showed median in the HC=1416.89pg/mL (range 430.22-1416.89), GBC= 1217.6pg/mL (range 650-1875.2), control= 394.5pg/mL (range 4.5-3197) with statistical significance between both groups vs control (P< 0.0001). The median serum levels of Gal-1 in the HC= 2669pg/mL (range 259-106213.33), GBC=13240pg/mL (range 1149-60040), control= 2431.43pg/mL (range 31.43-35117.14) without statistical significance between HC vs control (P=0.4562), but with significance between GBC vs control (P<0.0431). Only one patient had detectable Gal-12 in the HC= 0.723ng/mL, none in the GBC group and two patients in the control group (range 0.53-0.73) without significance between the groups. Conclusions- Patients with HC and GBC have serum levels of Gal-4 more than 4x higher than the control. Gal-1 levels are 6x higher in patients with GBC than the control group, but there is no difference from the HC's patients. Gal-12 is minimally detected in the 3 groups studied.

Acknowledgment: FACEPE, NUPIT-SG.

Pharmacological evaluation of the isatin-thiazole derivative (LAB-1E) in pancreatic neoplastic cells

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Background: Pancreatic Ductal Adenocarcinoma (PDAC) is the most common and lethal type of pancreatic cancer. The absence of early diagnosis, and resistance to chemotherapeutic agents lead to a high mortality rate, which makes the search for new therapeutic strategies extremely important. Thus, the present manuscript describes the in vitro evaluation of the isatin-thiazole derivative (LAB-1E) in PDAC cell lineages. Methods: The cytotoxicity of LAB-1E was evaluated by MTT, in peripheral blood mononuclear cells (PBMCs) and in PDAC lineages (BxPC-3, MIA PaCa-2 and PANC-1) from 1, to 100μM. DMSO (0.1%) was used as control. In addition, clonogenic assay, cell cycle interference, apoptosis, and caspase 3/7 activation were also evaluated. Results: The LAB-1E derivative was not toxic to PBMCs up to 100uM, on the other hand, it showed cytotoxicity in the BxPC-3 and MIAPaCa-2 lineages having an IC50 of 1.22μM and 5.22μM, respectively. Those concentrations were used for the subsequent tests. The compound significantly reduced colony formation (p<0.05) and cell proliferation. In addition, LAB-1E has promoted a significant (p<0.05) increase in cell death, cycle cell arrest in S/G2/M phases and increase in caspase 3/7 activity, suggesting cell death by apoptosis. Conclusions: The LAB-1E derivative was non toxic to PBMCs, cytotoxic to the BxPC-3 and MIAPaCa-2. In addition to reducing proliferation and clonogenic formation, interfering with the cell cycle and inducing apoptosis. Thus, the compound can be considered to in vivo evaluation as a possible pancreatic antineoplastic therapy. Acknowledgment: FACEPE, NUPIT-SG, CNPq

Single nucleotide polymorphism of the lgals1 gene and susceptibility to chikungunya infection and joint pain chronification

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Introduction: Chikungunya virus (CHIKV) is the etiologic agent of Chikungunya Fever (CHIKF), a disease characterized by fever, headache, and persistent joint pain. Efforts have been made towards understanding the mechanisms that causes joint damage, including the participation of galectins. These proteins regulate lymphocytes and macrophages cell functions and have a relevant role in the inflammatory process. Aim: To determine the allelic frequency of polymorphisms in the regulatory region of Galectin 1 gene (LGALS1) (rs4820293, rs4820294, and rs13057866) and evaluate their association with CHIKV infection susceptibility and chronicity. Methods: Peripheral blood samples from 215 positive CHIKF patients from the Biorepository of the REPLICK network (Clinical and Applied Research Network in Chikungunya) were used. The genomic DNA was extracted and quantified before real-time PCR genotyping (TaqMan detection method). Data were statistically analyzed using Pearson's Chi-Square Test. Results: The allele frequencies of the rs4820293 and rs4820294 polymorphisms were in Hardy-Weinberg equilibrium (X^2=0.699, p-value=0.40 and X^2= 2.440, p-value= 0.12, respectively). In contrast, genotyping data from rs13057866 revealed a genotypic distribution of 0.46% A/A (n=1), 3.72% A/G (n=8), and 95.81% G/G (n=206), with an allele distribution of 0.03 for the A allele and 0.97 for the G allele, resulting in X^2= 7.03 and p-value 0.008. This implies in an association between the allele variant and the increased susceptibility of Chikungunya infection. In addition, it was possible to observe that the rs13057866 polymorphism is associated with the chronicity status of patients, if considering a significance level of 10% (X^2 5.367, p-value 0.068). Conclusion: The LGALS1 genotypic variations of rs4820293 and rs4820294 are in Hardy-Weinberg equilibrium and are not related to an increased risk of developing chikungunya fever. However, the rs13057866 variant is related to an increased susceptibility to chikungunya fever as well as a higher risk of chronicity of that disease.

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