12. Drug Discovery and Development

12.001 Pharmacokinetics of linalool complexed with B-cyclodextrin: **Is it a new therapeutic formulation for treatment of hypertension?** Camargo SB[1], Medeiros CFA[1], Santos VV[2], Azeredo FJ[3], Vasconcelos DFSA[1] [1]Fiocruz, [2]USP, [3]UFBA

Introduction: Hypertension is an important public health problem and natural products have demonstrated biological activities which can help in the control of this disease. Previous studies by our research group have demonstrated experimental evidence that linalool (LIN) has antihypertensive activity. LIN is an alcoholic monoterpene, present at essential oil, but have administration restrictions. Cyclodextrins, specially beta-cyclodextrin (β-CD), have a lipophilic structure inside and hydrophilic at periphery, which makes an ideal and favorable environment to formation of inclusion complexes and controlled drug delivery systems, improving bioavailability and effects of monoterpenes. **Aim:** The study aimed to investigate the pharmacokinetics of the LIN, a potential antihypertensive drug, administered as a free drug or complexed beta-cyclodextrin **Methods:** This study was approved by the Ethics Committee under the protocol CEUA-ICS/UFBA n° 085/2015. Free LIN and LIN/β-CD (100 mg/kg) were administered to male wistar rats by oral route and plasma concentrations were determinated by a validated HPLC-UV method. Blood samples were collected by the caudal vein at predetermined times after administration of the compounds. Individual profiles were evaluated by non-compartmental analysis using Excel®. The individual and mean PK parameters of elimination rate (ke), absorption rate (ka), clearance (CL), volume of distribution (Vd), half-life (t1/2), mean residence time (MRT), area under the curve (ASC), absolute bioavailability (Fabs) and relative bioavailability (Frel) were estimated for each animal. **Results:** The results of the parameters are respectively: free linalol (mean ± SD): ke (h-1) 0.09±0.06; t1/2 (h) 8,64±4,44; ASC 0-t (µg*h/ml) 0.04± 0.02; MRT (h) 1.97±0.65; MAT (h) 4.69±1.50; ka (h-1) 0.23±0.07; Cl (L/h/kg) 23.06±2.27; Vd (L/kg) 16.29± 10.73; Fabs 0.003±0.001; Frel not detected. As for the oral LIN/B-CD complex (mean ± SD): ke (h-1) 0.20± 0.19; t1/2(h) 12,08±14,27; ASC 0-t (µg* h/ml) 90.34±34.36; MRT(h) 2.20± 0.64; MAT(h) 6.28± 0.64; ka (h-1) 0.16± 0.01; Cl(L/h/kg) 1.27±0.55; Vd(L/kg)17.57±18.84; Fabs 1,26± 0,48; Frel 19.53± 7.42. The oral bioavailability of the LIN/B-CD complex was approximately 20-fold of the free LIN. **Conclusion:** Based on these results, these results demonstrated that linalool, once included in β-cyclodextrin, has increased bioavailability and it can be used as a new pharmaceutical formulation to treat hypertension in the future. **Financial Support:** CNPq, Capes. **Keywords:** Pharmacokinetic; Ciclodextrins; Linalool; Cardiovascular, Hypertension.

12.002 Preclinical pharmacological evaluation of *Senna velutina* **roots**: **Chemical composition**, *in vitro* **and** *in vivo* **antitumor effects**, **and death mechanisms in B16F10-Nex2 melanoma cell**. Castro DTH[1], Campos JF[1], Damião MJ[1], Torquato HF[2], Paredes-Gamero EJ[3], Carollo CA[3], Rodrigues EG[2], Souza KDP[1], Santos EL[1] [1]UFGD, [2]Unifesp, [3]UFMS

Introduction: Cutaneous melanoma is among the most aggressive types of cancer, and its rate of occurrence increases every year. Current pharmacological treatments for melanoma are not completely effective, requiring the identification of new drugs. As an alternative, plant-derived natural compounds are described as promising sources of new anticancer drugs. In this context, the objectives of this study were to identify the chemical composition of the ethanolic extract of *Senna velutina* roots (ESVR), to assess its *in vitro* and *in vivo* antitumor effects on melanoma cells, and to characterize its mechanisms of action**. Methods:** For these purposes, the chemical constituents were identified by liquid chromatography coupled to high-resolution mass spectrometry. The *in vitro* activity of the extract was assessed in the B16F10-Nex2 melanoma cell line using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and based on the apoptotic cell count; DNA fragmentation; necrostatin-1 inhibition; intracellular calcium, pan-caspase, and caspase-3 activation; reactive oxygen species (ROS) levels; and cell cycle arrest. The *in vivo* activity of the extract was assessed in models of tumor volume progression and pulmonary nodule formation in C57Bl/6 mice. **Results:** The chemical composition results showed that ESVR contains flavonoid derivatives of the catechin, anthraquinone, and piceatannol groups. The extract reduced B16F10-Nex2 cell viability and promoted apoptotic cell death as well as caspase-3 activation, with increased intracellular calcium and ROS levels as well as cell cycle arrest at the sub-G_0/G_1 phase. *In vivo*, the tumor volume progression and pulmonary metastasis of ESVR-treated mice decreased over 50%. **Conclusion:** Combined, these preclinical pharmacological evaluation show that the ethanolic extract of *Senna velutina* roots had *in vitro* and *in vivo* antitumor effects, predominantly by apoptosis, thus demonstrating its potential as a therapeutic agent in the treatment of melanoma and other types of cancer.

Support by: Fundect, CAPES and CNPq

12.003 Experimental Hydroxymethylnitrofurazone-therapy in CL-Brener bioluminescent *Trypanosoma cruzi* **infections is more efficient**, **reduces cardiac and hepatic damage in the chronic than acute stage**. Scarim CB[1], Francisco A[1], Jayawardhana S[1], Lewis MD, Chin CM[2], Taylor MC[1], Kelly JM[1] Unesp-Araraquara, FCFAr-Unesp

Chagas disease is an endemic zoonosis in countries of Latin America, resulting from infection by the hemoflagellate parasite called *Trypanosoma cruzi*(*T. cruzi*). Hydroxymethylnitrofurazone (NFOH), active against *T. cruzi* parasites *in vitro* and *in vivo* tests (acute and chronic), stands out. The purpose of this work was toevaluated the effects of NFOH *in vivo* studies (Balb/c) using CL-Brener bioluminescent strain. In this protocol, during the acute phase murine model, the treatment with NFOH (100mg/kg^{-1}/5 days) was able to suppress the parasites. However, after the first cycle of cyclophosphamide immunosuppression (200mg/kg^{-1}), five animals of six were negative. In the second cycle of immunosuppression, 100% of the animals reactivated, a result similar to BZN (100mg/kg^{-1}/5 days). Histological analysis (acute stage) showed that NFOH reduced cardiac fibrosis compared to the positive control and BZN as well as the amount of inflammatory infiltrates in the liver, values significantly different from BZN. In a chronic phase murine model, using a CL-Brener bioluminescent strain, treatment with NFOH (100mg/kg^{-1}) showed 100% cure of the animals, remaining unchanged after two cycles of immunosuppression with cyclophosphamide (200mg/kg^{-1}). After the 3rd cycle, reactivation was performed in two of the six animals analyzed, confirming 50% cure by the *ex vivo* assay. BZN (100mg/kg^{-1}), in the same protocol, showed 100% cure. Histopathological analysis (chronic stage), NFOH reduced the number of inflammatory infiltrates and cardiac fibrosis, moreover, in the liver tissue was able to reduce the amount of inflammatory infiltrates and total collagen values significantly different from BZN, demonstrating that NFOH is less toxic than BZN.The results demonstrated the potential effect of NFOH as promise anti-*T. cruzi* drug candidate. Further studies with more days' treatment and also in association with benznidazole (lower doses) will be done to goal the sterile cure with low toxicity. **Keywords:** Chagas disease, *T. cruzi*, Hydroxymethylnitrofurazone, benznidazole, *T. cruzi* bioluminescent **Financial support:** This work was financed in part by the Coordenação de Aperfeiçoamento Pessoal de Nível Superior - Brasil (CAPES) - finance code: 001; and, the Programa de Doutorado Sanduíche no Exterior (PDSE) – finance code: 88881.189584/2018-01. The authors would like to thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP - 2016/10847-9) by the research fellowships assistance and the LSHTM Biological Services Facility staff for technical support.

12.004 Evaluation of interaction between Nanocarrier PAMAM of 3rd generation and substance with potential anti-cancerigene. Silva MPG, Santos JCN, Araújo Júnior JX, Aquino TM, Abreu FCD UFAL

Introduction: Guanylhydrazone are a class of compounds that exhibit promising pharmacological activities. They have mixed properties (receptor and donor) in the formation of hydrogen bonds because they originate from the same chemical group as aminoguanidine. The efficient action as an anticancer agent for breast cancer, colon and human gliobastoma cells has been reported giving greater prominence to its derivativesT he association of the class with a biocompatible nanocarrier, Poly (amidoamine) 3rd generation (PAMAMG3), makes possible, among other factors, an improvement in the solubility of the substance and consequently its bioavailability and dose/effect relation in a future application. Such interaction is seen by means of electrochemical techniques. Objective**:** To evaluate the interaction of the derivative LQM10 with PAMAM G3 in different electrodes modified by electrochemical techniques**. Methods:** The electrochemical system was composed of 4 electrodes (two working electrodes), Ag/AgCl/Cl^-saturated (reference), platinum (auxiliary), vitreous carbon (CV) (work), gold (Au) (work), modified with carbon nanotubes (NTC) and PAMAMG3. An additional system was used composed of ITO-nanoparticles of gold-cysteamine-PAMAMG3, functioning as working electrode. The measurements were buffered at pH 7.02 with a co-solvent. **Results:** The LQM10 has a reversible oxidation peak with potential of ± 0.22V; By varying the concentration of LQM10 in solution it was possible to terminate through the derivative of the Langmuir[2] isotherm the interaction constant of the compound in front of the NTC-PAMAMG3 sensor in CV, as the value K_F= $1.23x10^6$ L / mol, characterizing the affinity of the compound as the CV-NTC-PAMAM3G sensor. Similar to verify the profile of the LQM10 against the AU electrode modified with PAMAMG3 on its surface in an organized manner resulting in K_F = $3.64x10^5$ L / mol. An analytical curve using the ITO-nanoparticle-gold-cysteamine-PAMAMG3 electrode was performed obtaining high linear correlation with substance and apparent association constant K = $5.86x10^5$ L / mol. Conclusions**:** All modification methodologies were efficient in demonstrating the interaction of LQM10 with PAMAMG3, being an indicative for the use of the complex for biological studies. **Key-words:** Guanilhidrazona, PAMAM, Cancer, eletroquímica **Financial support:** CNPq, CAPES and FAPEAL. [1]FRANÇA, P.H.B, et al, Acta Pharm., 66, 129, 2016 [2]SILVA, M.P.G, et al, Electrochim. Acta, 251, 442, 2017

12.005 Determination of the cytotoxic effect and evaluation of the *in vitro* leishmanicidal potential of new aminoguanidine hydrazone derivatives and other related compounds. Santos MS, Queiroz AC, Silva Júnior EF, Leite AB, Vieira ACS, Silva JKS, Aquino TM, Araújo Júnior JX, Moreira MSA UFAL

Introduction: According to data from the World Health Organization, Neglected Tropical Diseases affect more than one billion people worldwide. Among them, leishmaniasis is responsible for affecting more than 12 million people, with an average of two million new cases annually in the five continents, thus representing a serious public health issue. Until the moment, the available drug therapy is not ideal, given that drugs have significant adverse effects, long therapeutic regimens, and the fact that most of them require parenteral administration. In this sense, the search for new therapeutic alternatives becomes essential. This work, then, aimed to determine the cytotoxic and leishmanicidal activity of new aminoguanidine hydrazine derivatives and other related compounds. **Methods**: Initially, the cell viability assay was performed using the MTT reduction method. Subsequently, the derivatives were submitted to the test against amastigote forms of *Leishmania infantum chagasi*. **Results**: it was possible to observe that the tested derivatives did not show cytotoxicity up to the maximum tested concentration, 10 µM. Furthermore, it was also seen leishmanicidal activity with Maximum Effect (ME) above 50% and Inhibitory Concentration 50% (IC_{50}) below10 µM, which could be compared to the standard drug pentamidine which had a maximum effect of 67.3% and IC_{50} of the 4.4 µM. There was one aminoguanidine hydrazone derivative, LQM 55 – ME: 63.5%, IC_{50}: 7.7 µM, one heterocyclic aromatic guanylhydrazone derivative: LQM 195 – ME: 5.3%, IC_{50}: 0.06 µM, and three thiosemicarbazone derivatives: LQM 08.1 – ME: 56.9%, IC_{50}: 8.73 µM; LQM 95.1– ME: 60.2%, IC_{50}: 1.6 µM, and LQM 106.1 – ME: 60.4%, IC_{50}: 3.2 µM. **Conclusion**: In conclusion, it is valid to deepen the studies using the six derivatives which showed leishmanicidal activity against amastigotes of *Leishmania infantum chagasi*. Next studies may include the evaluation of the mechanisms of action and the leishmanicidal activity against other species of *Leishmania*, thus seeking the compounds which may become future drug prototypes. Supported by: Thanks, CNPq, CAPES, FAPEAL, INCT-INOFAR

12.006 From Kefir proteome to *in vivo* analysis: **Exploring the hypotensive effects of a prototype candidate for ACE inhibitor drug**. Amorim FG[1], Coitinho LB[2], Aires R[3], Dias AT[3], Meyrelles SS[3], Rezende LCD[3], Pauw ED[4], Quinton L[4], Campagnaro BP[1], Vasquez EC[1] [1]UVV-ES, [2]FCFRP-USP, [3]UFES, [4]University of Liège

Introduction: Kefir is a probiotic beverage prepared by milk fermentation and its consumption has been associated with several beneficial effects, including antihypertensive action. However, the bioactive molecules responsible for this activity remain unclear.Therefore,proteomics methodologies were applied in order to identify the potential bioactive peptides in Kefir and we performed a bioprospection of thehypotensive action of a peptide (Kef-1)in the treatment of hypertension. **Methods:** For the proteomic study, Kefir and non-fermented milk were analysed by MALDI-TOF and Shotgun Proteomics. Samples were coprecipitated with 1µL of 2,5-dihydroxybenzoic acid matrix and analyzed in MALDI-TOF UltrafleXtreme (positive mode reflected). For shotgun proteomics, 20 µg of sample was reduced with dithiothreitol followed by alkylation with iodoacetoamine and subjected to digestion with trypsin. Digests were analyzed by Q-Exactive Orbitrap mass spectrometer and followed by the analysis in the software Peaks Studio v8.5. *In silico* tools were used to predict the physical-chemical features of the peptides and molecular docking in the angiotensin-converting enzyme (ACE) were performed. Peptides with potential ACE-inhibitory (ACEi) activity were synthesized by AminoTech and tested for *in vitro* ACEi activity. *In vivo* analysis was performed in mice (C57Bl/6J, males) which were subjected to clipping of the left renal artery (2K1C). After measurement of blood pressure (BP) by tail plethysmography, the animals were divided into 2 groups: 2K1C vehicle (water) and treated-2K1C(10 mg/kg, v/v). Sham animals underwent surgery without clipping of the renal artery. Acute treatment was performed by the measurements of BP 3 h after a single administration by gavage of Kef-1 (Animal Ethics Committee-UVV approvals #489-2018). Data are reported as mean±SEM and one-way ANOVA (Tukey's test) was used. Level of significance was fixed in $p<0.05$. **Results:** The ions profile overview obtained by MALDI-TOF revealed an increase of new peptides after fermentation. Shotgun proteomics allowed to sequence these peptides and after analysis against the databases, 35 peptides with potential antihypertensive activity were selected. These peptides had their physical-chemical features predicted and one of them, named Kef-1, presented a favourable interaction with ACE. Kef-1 was able to interact in a manner similar to enalapril at key points for ACEi. The ACEi of Kef-1 was confirmed *in vitro* (72.3% inhibition relative to captopril)and *in vivo*, whereas Kef-1 was able to reduce the mean BP and systolic BP ($\Delta 19.6 \pm 6.8$ mmHg; $\Delta 26 \pm 5.9$ mmHg respectively; $p<0.05$) in the group treated-2K1C compare to controls. **Conclusion:** These results demonstrated the benefits of Kefir products and can guide the development of new prototypes candidates for antihypertensive drugs. **Financial support**: CNPq (150037/2018-0), FAPES, CAPES and FAPESP.

12.007 Use of the ethanolic extract of *Mimosa tenuiflora* for the synthesis of silver nanoparticles with antimicrobial applications. Souza JMT, Rocha LMC, Barros AB, Araújo AR, Silva DA, Marinho Filho JDB, Araújo AJ UFPI

Introduction: The rise of antimicrobial resistance has pointed to the necessity of searching for new antimicrobial agents. Natural products have always been used as a source of bioactive compounds with great potential. The use of plant extracts for the synthesis of nanoparticles has been seen as an alternative for the harmful chemical methods used, as well as to improve their biological potential. *Mimosa tenuiflora*, popularly known in Brazil as "Jurema Preta" (JP), is widely used in traditional medicine as an antinociceptive, anti-inflammatory and antimicrobial agent. This study aimed to use J Pethanolic extract as a reducing and stabilizing agent in the synthesis of silver nanoparticles (AgNPs) for antimicrobial applications. **Methods:** For the synthesis of AgNPs, different concentrations of the JP extract were prepared (0.1%, 0.05% and 0.025%) and left under constant stirring, at room temperature, until complete dissolution. After that, $AgNO_3$ (1mM - 1: 1 v/v) was added to the extracts solutions and the pH was adjusted to 7, by adding NaOH (2 M). The final solutions were left under the same conditions previously mentioned for 24 hours. Samples were characterized by Uv-vis spectroscopy and Dynamic Light Scattering (DLS). The antimicrobial potential of the JP-AgNPs was investigated by the determination of the Minimum Inhibitory Concentration (MIC), against four strains: *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922. **Results:** As soon as the solutions pH was adjusted, a colour change was observed and the solution passed from light-yellow to brownish, indicating the silver reduction and, consequently, the nanoparticles formation. This data was confirmed by the UV-vis spectroscopy, which showed the presence of plasmonic bands between 400 nm and 450 nm, varying according to the concentration of the extracts. This result indicates that the method applied was efficient for obtaining AgNPs in all the extract concentrations used. The DLS technique revealed the presence of nanoparticles populations with sizes varying from 185 to 225 nm and polidispersity indexes (PDI) from 0.2 to 0.5. The sample produced with 0.05% of extract presented the smallest AgNPs, but it is important to highlight that the PDI decreased as the extract concentration increased, suggesting that higher concentrations of extract provide more homogeneous AgNPs. The antibacterial assay showed that all the samples synthesized were able to inhibit bacterial growth, with MICs varying from 250 µg/mL to 31.25 µg/mL. Once more, the 0.05% sample stood out, meaning that smaller nanoparticles may have stronger antibacterial activity. **Conclusion:** In this study, the ethanolic extract of JP was successfully used for the pH-controlled synthesis of AgNPs, in a solvent-free method, for antimicrobial applications. The results showed that the extract concentration directly influences the nanoparticles formation, as well as their biological activity. Further studies are necessary to investigate their biocompatibility and mechanism of action. **SUPPORT**: Capes, CNPq, INCT BioNat.

12.008 Pharmacological screening of synthetics neolignans front of clinical bacteria strains. Dourado TMH, Cruz LS, Oliveira BHM, Oliveira BTM, Silva LAA, Rodrigues LC, Vasconcelos UVRG, Travassos RA UFPB

Introduction: The spread of antibiotic-resistant bacteria poses a substantial threat to morbidity and mortality worldwide (Taccanelli, Lancet. Infect. Dis., v. 18, p. 318, 2018). There is an urgent need to address the lack of effective treatments to meet the increasing public health burden caused by multidrug-resistant bacteria (Freire-Moran, Drug. Resist. Updat., v. 14, p. 118, 2011). Lignans and neolignans are a large group of natural products derived from the oxidative coupling of two C6–C3 units. This group of molecules possess many pharmacological activities described and they have been used for a long time both in ethnic as well as in conventional medicine (Teponno, Nat. Prod. Rep., v. 33, p. 1044, 2016). This study aims to investigate a possible antimicrobial effect of four neolignans obtained by organic synthesis, (E)-2-methoxy-4-(7-methoxy-3-methyl-5-(prop-1-en-1-yl)-2,3-dihydrobenzofuran-2-yl)phenol (Licarin A), 2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methyl-2,3-dihydrobenzofuran-5-carbaldehyde (4-O-Demethylkadsurenin M), (E)-2-(3,4-dimethoxyphenyl)-7-methoxy-5-(prop-1-en-1-yl)-2,3-dihydrobenzofuran (Acuminatin) and 1-(2-(3,4-dimethoxyphenyl)-7-methoxy-3-methyl-2,3-dihydrobenzofuran-5-yl)propane-1,2-diol (Licarinediol A) in three strains of clinical bacteria. **Methods:** Bacterial suspensions were standardized in sterile 0.9% NaCl solution from a fresh culture standardized by tube number 1 of the MacFarland scale (≈ $3x10^8$ CFU / mL). The minimum inhibitory concentration made in 96 well plates was analyzed with serial dilutions of the substances in the presence and absence of the microorganisms. The growth pattern was evaluated through optical density using absorbance microplate reader (BioTek ELX800) and data analyzed with ANOVA. Graphs were obtained by the program Graphpad Prism 6.0. **Results:** It was observed that the four drugs inhibited Escherichia coli (UFPEDA224) and Pseudomonas aeruginosa (UFPEDA416) with a high minimum inhibitory concentration (MIC). However, all drugs showed bacteriostatic effect against *Staphylococcus aureus* (UFPEDA02) in all concentrations analyzed. **Conclusion:** The four drugs were efficient only against UFPEDA02 strain.

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12.009 Anti-Inflammatory activity in arthritis model of nerolidol in inclusion complex with beta-cyclodextrin. Ribeiro LD[1], Souza EPBSS[1], Gomes MVLD[1], Silva LAS[1], Quintans LJ[1], Rocha LM[2], Cavalcanti MD[1], Araújo AAS[1] [1]UFS, [2]UFF
Introduction: Nerolidolis a natural sesquiterpene thathas several biological activities evaluated, especially anti-inflammatory [1].A problem for its administration isthe high volatility and low solubility resulting in considerable loss of oral bioavailability [2].In this context, β-cyclodextrin (β-CD) inclusion complex may promote the solubility of the formulation in aqueous solution, increasing its bioavailability and reducing the administrated dose. Considering the anti-inflammatory activity, it is believed that the complexation of this terpene may potentiate its action orally. Therefore, the objective of this study is to develop and characterize Nerolidol-loaded β-cyclodextrin and evaluate its activity on zymosan-induced arthritis model in mice**. Methods:** Inclusion complex was prepared by freeze-drying method [3], and characterized by Scanning Electron Microscopy (MEV), X-ray diffraction (XRD) and Nuclear magnetic resonance (NMR). In vitro toxicity was evaluated by MTT assay in IT76 cell line for 72 hours. In vivo neutrophils migration assay and histological analysis was performed on intra-articular zymozan-induced arthritis model in female Swiss mice [4] (protocol CEPA number 22/2018). **Results:** Nerolidol loaded β-CD showed Complexation efficiency 70%, MEV and XDR analysis suggests the complex formation. NMR confirmed by the proton difference of the inner cavity of the cyclodextrin. Formulations showed no toxicity under the conditions evaluated. Nerolidol-loaded β-CD 100µg/mL inhibited neutrophils migration into joint cavity to 35% compared with the control group. **Conclusion:** The data suggests that Nerolidol loaded β-CD improved its anti-inflammatory effect on arthritis in mice and reduced the needed dose of administration when compared to Nerolidol free. **References**: [1]Chan et al. Molecules, 21 (5) 2016; [2]Saito et al. J Pharm and Biom Anal 111 (2015);[3]Campos et al. Life Sciences229: 139-148, 2019; [4] Silva et al. Braz J Med Biol Res 51 (1) e6799, 2017. **Acknowledgements**: CAPES, CNPq, FINEP and FAPITEC/SE. Laboratory of Cellular Communication (Fiocruz) RJ, LaReMN-UFF.

12.010 Cardioprotective effects induced by alpha-terpineol from *Protium hepthaphyllum* **against myocardial infarction in rats**. Paulino ET[1], Rodrigues AKBF[1], Bernardino AC[1], Silva JCG[1], Machado MLDP[1], Oliveira KRV[1], Silva Júnior EF[1], Oliveira AP[2], Quintans-Júnior LJ[3], Ribeiro EAN [1]UFAL, [2]UFPI, [3]UFS

Introduction: Myocardial infarction is a common clinical outcome to mortality and morbidity of cardiovascular diseases previously (LÜSCHER, 2018). The complexity of infarction pharmacotherapy associated with the lack of cardioprotective drugs has encouraged the development of new cardioprotection strategies (HAUSENLOY et al, 2017). Thus, natural compounds have been represented candidate molecules for new drugs (NEWMANN& CRAGG, 2016). In this context, α-terpineol (TPN) is cyclic monoterpene as a major compound of essential oil of *Protium heptaphylum* produces cardiovascular effects (MOBIN et al, 2017). However, cardioprotective action of TPN remains unknown. The aim of this study wase valuate the cardioprotection effect of TPN on acute myocardial infarction in rats. **Methods:** This study was approved by ethics committee nº09/2015. Wistar-kyoto (WKY) and Spontaneously Hypertensive Rats (SHR) rats, were allocated on 7 experimental groups, were pre-treated for 15 days orally and induced to infarction by isoproterenol (ISO): (G1= saline 0.9% day); (G2= Infarcted saline 0.9% day); (G3= TPN 25 mg/kg/d); (G4=TPN 50 mg/kg/d); (G5=TPN 75 mg/kg/d); (G6=TPN 50 mg/kg/d without ISO) and (G7=Nifedipine (NIF) 3 mg/kg/d). On 16º day, rats were anesthetized (Ketamine 80 mg/kg + Xylazine 4 mg/kg i.p.) and biochemical, morphometric, histopathological, hemodynamic, baroreflex and electrocardiographic tests were performed. Cardiovascular tissues were used to determine calcium levels and to assess vascular reactivity. Additionally, the cardiovascular curve dose-response in hypertensive animals non-anesthetized with TPN was realized. Molecular docking was also accomplished. **Results:** TPN increased the survival of animals to induced infarction, reduced necrosis area of the myocardium, prevented changes to ischemia-reperfusion injury on electrocardiographic tests and inhibited the release of cardiac markers of myocardial damage and preserved histoarchitectural of hearts. Furthermore, TPN inhibited elevation of heart rate by ISO. TPN prevented the calcium overload in the ventricles and aorta. In addition, TPN produced coronary dilatation and endothelial neovascularization in vessels of rats. TPN also changes of the potency and maximal effect of vascular reactivity of hypertensive and infarcted rats. TPN induced dose-dependent intravenous bradycardia, which was significantly attenuated in the presence of a muscarinic receptor blocker. Molecular docking studies show that TPN has an electronic affinity to muscarinic M_2 receptors. **Conclusion:** TPN produces cardio protection in rats, and your mechanisms involved cardiac M_2 receptors. Finally, TPN was protected with patent by innovation and intellectual properties nº INPIBR 10.2019.004434-9 to TPN may be a cardioprotective drug candidate a new molecule for cardiovascular diseases. **Key-words:** Alpha-tepineol; Cardioprotection; Myocardial infarction; Monoterpenes. **Financial support:** CNPq, CAPES and FAPEAL. References: LÜSCHER, T.F. Epidemiology of cardiovascular disease: the new ESC Atlas and beyond. European Heart Journal v.39, p.489–492.2018. HAUSENLOY, D et al. Novel targets and future strategies for acute cardioprotection: Position Paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart. Cardiovascular Research, v.113, p.564–585. 2017. RIBEIRO,T.P. et al. Unravelling the cardiovascular effects induced by alpha-terpineol: a role for the nitric oxide-cGMP pathway. Clin Exp Pharmacol Physiol. V.37. p.1440-1681.2010. SABINO,C.K.B et al. Cardiovascular effects induced by alpha-terpineol in hypertensive rats .Flavor and fragrance journal. v.28, p.333-339. 2013. MOBIN, M et al. Gas Chromatography-Triple Quadrupole Mass Spectrometry Analysis and Vasorelaxant Effect of Essential Oil from *Protium heptaphyllum* (*Aubl.)March*.BioMed Research International.V.2017. p. 1-7.2017. NEWMANN, D.J & CRAGG, G.M. Natural Products as Sources of New Drugs from 1981 to 2014. Journal of natural products vol. 79, p.629-661. 2016.

12.011 Anticholinesterase-antimuscarinics: **Study of dual agents aiming at application for Alzheimer's disease**. Guimarães MJR[1], Viegas Júnior CV[2], Castro NG[1], Neves GA[1], Romeiro LAS[3], Nascente LC[3] [1]UFRJ, [2]Unifal, [3]UnB Alzheimer's disease (AD) is a progressive neurodegenerative disease that affects cognitive abilities mostly due to synaptic dysfunction and death of entorhinal, hippocampal and frontal cortical neurons. In the areas affected by AD there is a drop in the levels of acetylcholine, which contributes to impair cognition by reducing activation of nicotinic and muscarinic receptors. Aiming at restoring cholinergic neurotransmission, cognitive symptoms of AD are treated using anticholinesterase drugs, such as donepezil, galantamine and rivastigmine. However, the high cost and high incidence of side effects, mainly due to the activation of peripheral muscarinic receptors, drive the demand for new drugs. Two collaborative drug development projects yielded anacardic acid derivatives and phenylpiperidine donepezil analogues that were planned to have anticholinesterase activity associated with other beneficial activities in AD, such as anti-inflammatory and antioxidant. Among these novel substances we sought to discover an additional antimuscarinic activity, which might reduce peripheral adverse effects. Nighty nine substances were screened for their anticholinesterase effect and 28 were selected, showing IC50 between 2.8 and 29.7 μM for acetylcholinesterase and being non-competitive inhibitors. The anacardic acid derivative LDT532 at 10 μM was active in a M_3 receptor inhibition screening assay using Ca^{2+} fluorimetry in human colon epithelial cells (HT29). It also inhibited carbachol-induced bradycardia in isolated rat atrium, suggesting M_2 antagonism. Thus, LDT532 has both anticholinesterase and antimuscarinic activities, inhibiting M2 and M3 receptors that are the main targets of peripheral adverse effects of acetylcholinesterase inhibitors. Support: CNPq, CAPES, FAPERJ

12.012 Synthesis, **structural characterization**, **and antioxidant activity evaluation by DPPH method of Palladium-Benzodiazepine derivatives**. Silva AV, Meneghetti MR, Correia WBZGB UFAL

Introduction: Despite significant advances in medicine, epilepsy remains as one of the most common neurological disorders worldwide. The long-term therapy along with the simultaneous use of different drugs have limited the use of anticonvulsant drugs. Moreover, reports show that oxidative stress may be related to the pathogenesis of this disease, which indicates the importance of studies aiming the evaluation of the antioxidant activity of such drugs. Thus, the present study aimed to developnew compounds derived from benzodiazepines, such as diazepam, from the complexation of metals to these ligands, obtaining new metallodrugs candidates with biological potential – along with their structural characterization and evaluation of their antioxidant activity. **Methods:** Palladium(II) chloride and palladium(II) acetate were used as the main source of the metal in order to synthetize the dimeric palladacycles: $[(DZP)PdOAc]_2$, $[(DZP)PdCl]_2$, and $[(DZP)PdI]_2$ – the last one synthetized by halogen metathesis of $[(DZP)PdCl]_2$with potassium iodide. The compounds were characterized by Nuclear Magnetic Resonance (NMR), Fourier-transform Infrared Spectroscopy (FTIR), Mass Spectrometry (MS), and Elemental Analysis. After characterization, the compounds were submitted to an *in vitro* test in order to evaluate their antioxidant activity by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. **Results:** The synthetized compounds were wellcharacterized by the previous techniques mentioned, which confirmed the efficacy of the synthetic routes used. In the *in vitro* assay, the palladacycle coordinated to iodine – $[(DZP)PdI]_2$, showed a statistically decrease of DPPH ($p < 0.0001$) for all tested concentrations in the paladacycle coordinated iodine complex (100μM, 250μM and 500μM) when compared to free ligand control (diazepam) and DPPH.This effect may be associated with the formation of tri-iodine when the metal complex reacts with DPPH. Also, it was performed an evaluation of the necessary time to achieve this reduction, which showed that it occurs in the first 60 minutes of reaction. **Conclusion:** The synthesis of the dimers was effective to the formation of the palladacycles, which had their structures confirmed by different techniques. The antioxidant evaluation showed that the metal complex with iodine was able to statistically reduceDPPH in the tested concentrations. Furthermore, it is important to mention that new studies with oxidative stress biomarkers are necessary in order to effectively confirm the antioxidant potential of the synthetized complexes. **Financial Support:** CNPq, CAPES, and FAPEAL.

12.013 Cationic unilamellar liposomes as a drug carrier system to increase the efficiency of LQM168 - A Potential Antitumor Hybrid Molecule. Lins SL, Santos PFD, Aquino TM, Abreu FC UFAL

Introduction: Cancer is a group of diseases characterized by the disordered growth of abnormal cells. According to WHO, about 8.8 million people die every year in low- and middle-income countries due to these pathologies. A way to increase the survival of cancer patients have been studies conducted to make chemotherapy more effective. The advance in the knowledge of new molecules is one of the main tools used in the development of new drugs. Molecular hybridization has been highlighted as a rational strategy to obtain new molecules due to the possibility of potentialization the pharmacological effect, decrease toxicity and lower risk of pharmacological interaction. In addition, the development of methodologies that increase the bioavailability of these compounds, as well as their release in the local target, is extremely important; Thus, liposomes occupy a prominent position as drug carriers because of their biocompatibility, structural variability and because they are highly functional, thus allowing the association of structures independently of their charge or molecular mass. **Objective:** To synthesize, characterize cationic unilamellar liposomes and to analyze the formation of inclusion complexes with compound LQM168 (which presents the quinoline and thiazolidine nuclei with proven antitumor activity) using spectroscopic and electrochemical techniques. **Methods:** Cationic unilamellar liposomes with and without LQM168 were synthesized by the lipid film hydration method and were characterized using DLS, UV-VIS, fluorescence spectroscopy, and FTIR. The electrochemical studies for LQM 168 were performed in aprotic medium (DMF + TBAPf6) and in protic medium (PBS pH: 7.0),using a three electrodes system with a conventional cell (working electrode: glass carbon, reference: Ag | AgCl | $Cl^-_{(sat)}$, counter electrode: platinum wire.) Electrochemical interaction studies between LQM168 and liposomes were performed in an aqueous medium.**Results:** LQM168 shows a reversible electrochemical behavior with redox potential favorable for physiological processes of electron transfer (Epa: -0.056V and Epc: -0.085V). As a result of the electrochemical studies, it was possible to evaluate the mechanism of action of LQM 168. The interaction studies between LQM 168 and liposomes by UV-vis demonstrated that the band at 415 nm was suppressed as well a bathochromic shift. Through fluorescence technique, it was possible to evaluate the interaction by a reduction of the light intensity, when using liposomes. **Conclusion:** cationic unilamellar liposomes as a carrier for LQM 168 is quite promising. Complex formation between these two compounds demonstrated an increase of the molecule stability and solubility in the aqueous medium. The use of electrochemical techniques on the interactions studies was quite satisfactory and accurate, showing to be a highly promising technique to studies of this nature. Key words: Lipossomes, Quinoline-thiazolidine, Cancer, electrochemistry **Financial support**: CAPES e FAPEAL. 1 HE, K. et ai., chemico-biologicalinteractions., 295, 13-19, 2018 2 TABARES, J.S.F et al., Electrochimica. Acta, 56, 10231-10237, 2011

12.014 Synthesis, **structural characterization**, **and evaluation of anticonvulsant and antioxidant activities of Diazepam-Palladium**(**II**) **complexes**. Correia WBZGB[1], Reys JRM[1], Oliveira MA[2], Gouveia DN[2], Quintans JSS[2], Quintans-Júnior LJ[2], Silva AMO[2], Gatto CC[3], Meneghetti MR[1] [1]UFAL, [2]UFS, [3]UnB

Introduction: Epilepsy is a neurological disease that affects approximately 50 million people worldwide and is related to oxidative stress, which plays an important role in the neuronal damage induced by seizures. The current drugs used in the treatment of this disease have their use of ten limited due to their adverse effects; moreover, approximately 30% of epileptic patients who are receiving drug treatment are not totally free of seizures. These facts motivated the development of this work that aims to synthesize, characterize and evaluate palladium(II) complexes derived from diazepam in order to obtain complexes that can be used to treat epilepsy**. Methods**: In this work were synthesized five complexes of diazepam-palladium(II). Two dimeric complexes, $[(DZP)PdCl]_2$ and $[(DZP)PdOAc]_2$, were obtained via cyclopalladation of diazepam, using either $PdCl_2$ or $Pd(OAc)_2$ salts as palladium sources. Three monomeric complexes, (DZP)PdOAcPy, (DZP)PdClPPh_3 and (DZP)PdOAcPPh_3, were obtained via coordination of Lewis bases, pyridine and triphenylphosphine, with the dimeric complexes. All these complexes were characterized by spectrometric techniques and elemental analysis; the$[(DZP)PdOAc]_2$ dimer had your chemical structure elucidated by X-ray diffraction. In addition, all complexes were evaluated for anticonvulsant and antioxidant activities. The anticonvulsant potential of the complexes was evaluated through pentylenetetrazole-induced convulsions model. The antioxidant activity was evaluated through oxidative stress biomarkers (activity of the antioxidant enzymes superoxide dismutase and glutathione peroxidase, and FRAP assay, reduced glutathione content, lipid peroxidation and quantification of the proteins). This work was approved by Animal Ethics Committee of the Tiradentes University (010817).**Results:** Through the characterization techniques used in this work it was possible to confirm the formation of all the complexes; it is important to note that the X-ray diffraction study of $[(DZP)PdOAc]_2$ showed the distorted square-planar geometry of palladium(II), the occurrence of cyclopalladation and the open-book shape of this dimer. Regarding the anticonvulsant and antioxidant activities, it was observed that the$[(DZP)PdOAc]_2$ dimer presented significant results. **Conclusion:** In this study five diazepam-palladium complexes were synthesized with good yields. The anticonvulsive effect and the potential neuroprotective effect performed by $[(DZP)PdOAc]_2$ should be emphasized, since they are important characteristics of new drugs for the treatment of epilepsy. **Financial support**: CAPES, CNPq, FAPEAL.

12.015 Evaluation of the anti-inflammatory activity of sulphatate polymeracids of seaweed *Hypnea musciformis*. Nascimento HG, Silva Junior PN, Soares VVM, Benevides NMB UFC

Metabolites extracted from seaweed, especially the sulphated polysaccharides have attracted interest because of its numerous biological properties, they are: anticoagulant (FIDELIS et al., 2014; ADRIEN et al., 2017), antioxidant (GUARATINI et al, 2012; MEDEIROS, 2015), antiviral (MA et al., 2016), immunostimulant (YANG et al., 2011), antimicrobial (BERRI et al., 2016), anticancer (MOGHADAMTOUSI et al., 2014) and anti-inflammatory (VANDERLEI, 2012; COURA et al., 2015; ARAÚJO et al., 2016). Therefore, this study aims to evaluate the anti-inflammatory activity of sulfated polysaccharides from seaweed *Hypnea musciformes* (PST-Hm). To achieve these objectives, PST-HM were extracted by proteolytic digestion (FARIAS et al., 2000), yielding the crude extract, and there was determined from the molecular weight and the yield of PST-Hm. Moreover, it was performed physico-chemical characterization of PST-Hm wherein the total carbohydrates (DUBOIS et al., 1956) were performed dosages, sulfate (DODGSON; PRICE, 1961) and possible contaminating proteins (BRADFORD, 1976). present in the sample. The anti-inflammatory activity of PST-Hm was assessed by paw edema test (CEUA No. 8116050518) induced by carrageenan (Cg) and dextran. The result of the physical-chemical characterization of PST-Hm revealed that the percentage of total carbohydrate and obtained sulfate was equal to 37,28% and 30,4%, respectively. In addition to the dosage of protein contaminants absorbance reading was below the detection power spectrophotometer employed, demonstrating that the material obtained in the enzymatic extraction contains only traces, or has no protein contaminants. Assessment of anti-inflammatory activity has shown that PST-Hm at doses 2.5, 5,0 and 10,0 mg/kg for anti-inflammatory effects in models of paw edema induced by carrageenan and dextran. The carrageenan-induced paw edema trial showed that the 5 mg/kg dose caused a 43.6% reduction in edema after the second hour of administration compared to the control group. For the paw edema trial performed with dextran, the dose of 5 mg/kg was effective in significantly reducing edema within 30 minutes after administration of the proinflammatory agent, with a reduction percentage of 31.5% when compared to the control group. The conclusion is that sulfated polysaccharides from seaweed *Hypnea musciformes* (PSTHm) possibly retain anti-inflammatory activity. Thus, it is expected to obtain an alternative source of natural compounds having anti-inflammatory action, which has efficacy and safety by minimizing the occurrence of side effects that limit the use of these drugs. Thanks: Federal University of Ceará (UFC) and carbohydrates and lectins Laboratory (Carbolec). **Financial support**: National Council for Scientific and Technological Development (CNPq).

12.016 Curcumin-nicotinamide cocrystal presents antinociceptive and anti-inflammatory activities in mice. Zilli GAL[1], Alves BO[1], Morgan LV[1], Ribas MM[2], Lanza M[2], Aguiar GPS[1], Oliveira JV[2], Müller LG [1]Unochapecó, [2]UFSC

Introduction: Curcumin is a polyphenol from*Curcuma longa* that presents anti-inflammatory effects related to its ability to reduce inflammatory transcription factors, enzymes and cytokines. The major limitations to the pharmacological use of curcumin areits low dissolution potential, low absorption, rapid metabolism and rapid elimination by the biological systems and, therefore, low bioavailability. The cocrystallization process is characterized by the incidence of molecular interactions between the active pharmaceutical ingredient and coformer, that enables improvements in physicochemical properties, such as solubility and bioavailability. The main advantages of supercritical carbon dioxide ($SCCO_2$) in cocrystallization are that is a green solvent, nontoxic, non-flammable and has moderate critical temperature and pressure. This work aimed to investigate the antinociceptive/anti-inflammatory activities of curcumin-nicotinamide cocrystal obtained by cocrystallization with $SCCO_2$. **Methods:** Male Swiss mice (25-35g) were used in the study(Animal Research Ethical Committee-Unochapecó approval: 008/19). The antinociceptive/anti-inflammatory effects of curcumin-nicotinamide cocrystal (0.5 mg/kg, p.o.), curcumin (0.5 mg/kg; 50 mg/kg, p.o.), nicotinamide (0.5 mg/kg, p.o.) and the positive control indomethacin (10 mg/kg, p.o.) were investigated in the acetic acid-induced writhing and formalin tests. Vehicle groups were treated (p.o.) with saline plus 1% polysorbate 80. The results were evaluated by one-way ANOVA *post hoc* Student-Newman-Keuls. **Results:** Curcumin-nicotinamide cocrystal (0.5 mg/kg p.o.) and curcumin (50 mg/kg p.o.) significantly reduced ($p<0.05$) the number of abdominal writhing compared to vehicle-treated and positive control groups ($F(5,28)=54.35$; $p<0.001$). In the formalin-induced nociception test, the positive control, curcumin(50 mg/kg p.o.)and curcumin-nicotinamide cocrystal (0.5 mg/kg, p.o.) significantly reduced the nociceptive behavior (s) in both phases (phase I: $F(5,28)=12.79$; $p<0.001$; phase II: $F(5,28)=35.40$; $p<0.001$) of the test when compared to the vehicle-treated group, and there were no differences between the nociception time of these groups. Conclusions**:** The curcumin-nicotinamide cocrystal was effective in the behavioral tests employed in this study, which demonstrates that in addition to maintaining the antinociceptive and anti-inflammatory properties of curcumin, the cocrystallization process increased the potency of curcumin, since the dosage of the cocrystal was reduced by 100 times. This probably occurs due to a change in the crystalline structure of the cocrystal, compared to curcumin, which positively changes its bioavailability. The mechanism of the cocrystal antinociceptive and anti-inflammatory activities and its effects on locomotor activity will be further studied. **Aknowledgements:** Universidade Comunitária da Região de Chapecó (PIBIC/FAPE) and Programa de Bolsas Universitárias de Santa Catarina – Uniedu (Art. 170 CE).

12.017 Structure-based nucleosome binding peptides for controlling cell function.
Fernandes VA, Teles KT, Torres IT, Treptow WT, Santos GS UnB
Introduction: The nucleosome surface has been hypothesized as a therapeutic target due to its capacity to modulate chromatin architecture. Herein, we rationalized that Nucleosome Binding Peptides (NBPeps) would be able to occupy the nucleosome surface directly, thereby modulating chromatin status and influencing phenotypic outcomes. **Methods:** First, we generated a new NBPep, GMIP1, with nucleosome surface binding capabilities that are highly DNA dependent. To understand how the nucleosome structure is modify by the binding of GMIP1 and other NBPeps derived from nucleosome binding proteins, we performed a series of structure-based calculations on the nucleosome surface interaction with NBPeps. **Results:** Biochemical assays corroborated the hypothesis that distinct NBPeps present differential actions on the final nucleosome structure despite binding to similar target regions on the nucleosome. Cell-based assays and fish models demonstrated that the NBPeps penetrate the cell and have specific effects on cell physiology and phenotypic outcome. **Conclusion:** Those results suggests that NBPeps might have important therapeutic implications. This work was supported by Conselho Nac. Des. Cient. Tecnologico (CNPq)

12.018 *In vitro* **antiviral activity of crude and fractioned extracts of** *Hypnea musciformis* **against Zika virus**. Gomes MVSW, Souza TPMS, Silva SLOS, Brito IRR, Guedes EAC, Bassi EJ, Rodarte RS UFAL

Introduction: Zika virus (ZIKV) belongs to the Flavivirus genus. It was first isolated in Uganda in 1947. In 2015 it was introduced in the Americas. Combating ZIKV has entered the World Health Organization "Blueprint list of priority diseases", whose function is to identify diseases that pose a risk to public health because of their epidemic potential and which are in countermeasures. The absence of specific drugs or vaccines for Zika justifies the encouragement of research for the development of antivirals. The aim of this research was to evaluate the antiviral potential of crude and fractionated extracts of *H. musciformis* in ZIKV-infected Vero-E6 cells. **Methods:** The MTT assay was used to assess the antiviral potential of the extracts of *H. musciformis* (EBD: crude extract dichloromethane, EBE: crude ethanolic extract, FCD: chloroform fraction of the crude dichloromethane extract and FHD: hexane fraction of the crude dichloromethane extract).The cells were incubated for 72 hours with and without the vírus, added at different times - pre-treatment and post-treatment -. The cytotoxic effect in peripheral blood mononuclear cells (PBMC) was also investigated according to this protocol (CAAE: 34140312.3.0000.5013). Statistical analyzes were performed using the One-Way ANOVA method, followed by Tukey and Dunnett's post-test with significance level $p < 0.05$. **Results:** The extracts of *H.musciformis* were tested in VERO-E6, allowing the obtention of a citotoxic concentration (CC50); EBD ≅100µg/mL, EBE ≅250µg/mL, FCD ≅100µg/mL and FHD ≅100µg/mL. In the antiviral assay, EBE was able to inhibit ZIKV at all concentrations tested (15 to 120µg/mL) pre-treatment and post-treatment. To ensure that EBE could be used as an antiviral agent with no harm for human cells, it was also tested in PBMC at 24 and 72 hours. A cytotoxic effect was only observed after 72 hours of treatment between 60µg/mL (63.82% viability of PBMC ±3.34) to 120µg/mL (40.80% viability of PBMC ±1.55). **Conclusion:** Among the four extracts tested, EBE hasshowned better antiviral activity for all tested concentrations, both pre-treatment and post-treatment. This foundings reinforces the need for assays that elucidate its mechanism against ZIKV-infected cells.