11. Clinical Pharmacology, Pharmacokinetics, Pharmacogenomics and Preclinical Toxicology

11.001 Development and characterization of multilamellar liposome pyridostigmine containing. Souza ACM[1], Neves NCV[1], Botacim WE[1], Frézard FJG[2], Souza J[1], Grabe-Guimarães A[1], Silva-Barcellos N M[1] [1]UFOP – DEFAR, [2]UFMG – Fisiologia e Biofísica

Introduction: Pyridostigmine bromide is an anticholinesterase drug used to treat *myasthenia gravis*. It presents cardioprotective activity is already demonstrated, however, its short half-life and the adverse effects may limit the long term use(Grabe-Guimarães, A*.; Clin. Auton. Res*.; 9, 83, 1999.). Liposomes are vesicles composed byphospholipids and they have the property of conveying hydrophilic and lipophilic active substances, and confer differentiated body distribution , stability and modification of drug interactions with the organism (Blume, G.; Biophys. Acta.; 1029, 91, 1990). The major advantage of these structures is allow the targeting of drugs to specific sites and slowly release of the encapsulated substance, thereby increasing the power and / or reducing their toxicity (Chonn, A.; Current. Biology.; 6, 698, 1995. Lasic, D.D.; Trends Biotechnol.; 16, 307, 1998.). This study aimed to develop and characterize liposomal formulation containing pyridostigmine . **Methods:** Liposomes composed DSPC :CHOL or DOPC and CHOL in a molar ratio 5:4 were prepared by the methodology of freeze / thawing (Nayar, R.; Biochim. Biophys. Acta; 986, 200,1989). An analytical spectrophotometric method was developed and validated for quantification of liposome-PIR and determination of encapsulation efficiency. The validation procedures were performed according to ANVISA Resolution RE No. 899 and criteria established by the International Conference on Harmonisation, ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH, 2005. Analyses of size and release of pyridostigmine from the formulations were also made. **Results and Discussion:** The spectrophotometric method was linear from 0.02 to 0.09 $mg.mL^{-1}$. The accuracy of this method was determined intra and inter-day, obtaining results as coefficient of variation between 1.73 to 2.72% and 0.32 to 2.32%, respectively. The accuracy ranged between 99.45 and 101.12%. The liposomal matrix did not influence the methodology of pyridostigmine detection . The proposed method demonstrated specificity, precision, accuracy and reproducibility being able to quantify pyridostigmine lipossomes. The encapsulation efficiency was determined as 23.4% and 15.4%, respectively. The results of analyses of size and release of pyridostigmine from the formulations showed that these are viable for future studies in vivo. Funding agencies: FAPEMIG and UFOP. Thanks: FAPEMIG, CNPq, UFOP and UFMG.

11.002 Behavioral pharmacological screening and acute toxicity of biofilm acetylated of manioc starch (BIOAC). Jesus DR[1], Espanhol CAA[2], Prando TBL[2], Sabatini DR[2], Gomes C[3], Lourenço ELB[4], Gasparotto Junior A[1] [1]UNIPAR – Ciência Animal, [2]UNIPAR – Farmácia, [3]UFPR, [4]UNIPAR/UFPR – Farmácia

Introduction: In recent year a new generation of biomaterials has been introduced as an alternative, is to apply edible films as dietary supplements or tablet excipient for purpose of controlled drug release. In addition, some edible films and coatings have been widely used for fresh fruits, vegetables, confectioneries, frozen foods, and meat products to improve their conservation. The biofilm acetylated from manioc starch (BIOAC) was effective for this application, therefore besides retaining all the natural characteristics of the food, it's easy to obtain, cheap and doesn't cause environmental damage. Even with all its apparent advantages, there isn't available date on the toxicity of this compound. So, we performed a behavioral pharmacological screening and acute toxicity of the BIOAC in Wistar rats. **Methodology:** Female and male rats (n = 6 per group) were orally (5000 mg/kg) and intraperitoneally (1000 and 3000 mg/kg) administered with a single dose of BIOAC for the observation of acute signs of toxicity until 14 days. After treatment, the animals were observed for the first hour, followed by every hour up to 6 h, and subsequently daily for 14 days. The observations comprised the behavior and manifestations of the toxic symptoms, and were carried out according to the Guidelines of the Organization for Economic Cooperation and Development (OECD, 1995). All procedures were approved by the Institutional Ethics Committee of the Universidade Paranaense (UNIPAR, Brazil; protocol number 20768/2011). **Results and Discussion:** The oral (5000 mg/kg) or intraperitoneal (1000 and 3000 mg/kg) administration of BIOAC in rats (both sexes) did not produce mortality or any behavioral disorders, after observation for 14 days. No unusual changes in locomotor activity, ataxia or signs of toxicity. There was no difference in body weight of rats treated with BIOAC compared with control animals. The results gathered in this study show the absence of acute toxicity of the BIOACin Wistar rats. However, other studies are necessary for a complete evaluation of the safety of this biofilm, as oral toxicity studies after repeated doses, genotoxicity and carcinogenicity studies. **References:** Organization for Economic Co-Operation and Development - OECD, 1995. Guideline for testing of chemicals. Guideline 407. Adopted 27th July 1995. Paris. Financial support: DEGPP/ Universidade Paranaense – UNIPAR.

11.003 High performance liquid chromatography method for determination of gemifloxacin in lung, **liver and kidney (microdialisates) of rats**. Pires CC[1], Grünspan LD[1], Lauriano JV[2], Araújo BV de[2], Tasso L[1] [1]UCS, [2]UFRGS

Introduction: The gemifloxacin (GEM) is a fluoroquinolone approved by the Food and Drug Administration (FDA) for the treatment of Community-acquired pneumonia or hospital acquired with mild to moderate against various microorganisms [1,2]. GEM is widely distributed throughout the body tissues after oral administration [3]. **Methods:** In this study we employed high performance liquid chromatography. Chromatographic resolution was achieved using RP- C_{18} column (Shimadzu Shim-Pack, 250 x 4.6 mm ID; particle size 5 µm) at a flow rate of 1.1 mL/min and an injection volume of 30 µL. All samples and standard solutions were chromatographed at 45 °C using triethylamine solution (0.5% v/v), adjusted to pH 3.0 ± 0.1 with 85% phosphoric acid, methanol and acetonitrile (71:15:14, v/v/v) as mobile phase. The detection wavelengths were set at 344 nm and 399 nm for excitation and emission, respectively. The analytical performance parameters evaluated were linearity, limit of quantification, precision and accuracy, obtained from standard curves and quality control. To demonstrate the applicability of the analytical method the microdialisate samples (lung, liver and kidney) were analyzed according to the method described above. The microdialisate samples were collected from male Wistar rats (250-300g) after a single intravenous administration of GEM 40 mg/kg by lateral tail vein. The project was approved by the Ethics Committee of the University of Caxias do Sul (#60/2009). MD recoveries were performed in lung, liver and kidney (n = 3). **Results and Discussion:** The retention time for GEM was approximately 6.5 min. The method was linear for drug concentrations ranging between 50 - 2000 ng/mL ($r \geq 0.99$). The limit of quantification was 50 ng/mL. The intra-day precision for quality controls ranged from 3.95% to 7.53% for day 1 and from 1.85% to 6.04% for day 2. The inter-day variation ranged from 1.05% to 4.09%. The accuracy was upper than 81.8%. The method was validated according to FDA Guidelines [4]. **Conclusion:** This analytical method using HPLC can be used to determine GEM in different matrices of rats. **References**: [1] HONG, C. Y. Farmaco. v. 56, p. 41, 2001 [2] FILE, T. M. Jr. Infect. Dis. Clin. North Am. v. 18, p. 993, 2004 [3] GRÜNSPAN, L. D. Chromatography. v. 75, p. 253, 2012 [4] FDA Guidance for Industry, Bioanalytical Method Validation, May 2001. **Acknowledgments and Financial Support:** FAPERGS, UCS

11.004 Assessment of *in vitro* and *in vivo* recovery of gemifloxacin using microdialysis. Grünspan LD[1], Pires CC[1], Laureano JV[2], Araújo BV de[2], Tasso L[1] [1]UCS, [2]UFRGS

Introduction: Gemifloxacin (GEM) is an advanced fourth generation fluoroquinolone with a broad-spectrum of antimicrobial activity that includes potent activity against *S. pneumoniae* and it is widely distributed in the tissues [1-2]. The application of the microdialysis technique to the investigation of pharmacokinetics of drugs requires careful assessment of the probes performance to ensure validity of the data obtained using this technique. *In vitro* and *in vivo* microdialysis probes calibration may be performed employing several techniques, such as extraction efficiency (EE) and retrodialysis (RD). The aim of this study was to determine *in vitro* and *in vivo* recovery of MD probes employing GEM. **Methods**: Microdialysis probes (CMA/20, 4 mm membrane length) and an infusion pump (Harvard PHD 2000) were used. Both *in vitro* and *in vivo* methods were employed to assess the relative recovery of the microdialysis probes. The *in vitro* recovery of GEM was determined by two different methods: EE and RD at 500, 1000 and 2000 ng/mL. Both methods were carried out at 37 ± 1 °C. Perfusion was made at different flow rates (1, 1.5 and 2 µL/min). For *in vivo* evaluation (male Wistar rats, 250-300g) only RD was employed. The microdialysis samples (microdialisates) were collected after a single intravenous administration of GEM 40 mg/kg by lateral tail vein. MD recoveries were performed in lung, liver and kidney (n = 3). The study protocol was approved by the Ethics in Research Committee of the University of Caxias do Sul (#60/2009). Dialysate samples were analyzed by HPLC. **Results and Discussion:** *In vitro* recovery of GEM from the microdialysis probe was independent on the concentration and stable over a 12-h period. Microdialysis recoveries determined *in vitro* by EE at 1.0, 1.5 and 2.0 µL/min were 42.12 ± 8.79%; 29.24 ± 3.67% and 25.11 ± 4.94%, respectively. For RD, microdialysis recoveries were 25.23 ± 3.13%; 23.67 ± 3.31% and 13.44 ± 0.59%, respectively. Comparable *in vitro* recoveries were obtained by different established approaches including recovery estimation by EE and RD at 1.5 µL/min. *In vivo* recoveries by RD (1.5 µL/min) in Wistar rats' kidney, lung and liver were 27.69 ± 2.09%, 23.12 ± 3.79% and 17.38 ± 0.68%, respectively. **Conclusion:** The *in vitro* and *in vivo* performance of the microdialysis technique was established for the study of GEM in tissues. **Acknowledgments and Financial Support:** PROBIC-FAPERGS (ARD project nº. 0901946) and BIC-UCS. **References:** [1] BALL P, Mandell L. Int J Antimicrob Ag. v. 23, p. 421-429, 2004. [2] DAVIES T. A. Antimicro Agents Chemother. v. 44, p. 304-10, 2000.

11.005 Do renal disease and carvedilol association modulate digoxin pharmacokinetic in patients with heart failure? Souza FC, Baptista TM, Neri JS, Gomes JPM, Oliveira GF, Nascimento TA, Scaramello CBV UFF – Farmacologia Experimental

Introduction: Knowledge of drugs' pharmacokinetic (PK) parameters in different patients is essential for safe therapeutics regimens establishment. Digoxin (DIG) is used in heart failure (HF) and constitutes an insecure drug due to its narrow therapeutic range-TR (Einarson *et al*. Can J Hosp Pharm. 42: 63, 1989; Bressler & Bahl. Mayo Clin Proc. 78: 1564, 2003). A retrospective study conducted at Instituto Nacional de Cardiologia (INC) showed that 647 patients were admitted to the HF ward along 2009-2010 and 194 of these individuals have used DIG. As unexpected, the digitalis plasma concentration (Cp) was measured in less than 50% of these patients (n = 80). Forty two individuals presented Cp out of the TR and the majority were males (n = 33), HF functional class-FC III (n = 27), presenting comorbidities such as renal failure (n = 19) and drug interactions, like carvedilol (n = 23) (Souza *et al*. FeSBE 2011, Abstract 15.006). The aim of our work is to conduct DIG PK studies in different patients with HF and then propose safe and individualized therapeutic regimens (INC and Hospital Universitário Antônio Pedro Ethics Committees id approval numbers: 0306/07-12-10 and 240/2010). **Methods:** Selected patients (male, FC III and IV) are included in the study after informed consent signature. Individuals using DIG 0,125-0,250 mg are grouped according to comorbidities and therapeutic combinations. Blood samples are collected at different times along 24 h after DIG oral administration. Measurement of digitalis Cp is performed using immuno-chemiluminescence method (LLOQ = 0,3ng/mL; precision≤10%). Graphic representation and PK parameters (Cmax, Tmax, AUC and CL/F) are being determined using Graph Pad Prism 5.0. Data are presented as mean and standard error of the mean and analyzed by Student *t* test. **Results:** Focusing on carvedilol association, it was possible to create groups I (without βblocker,n = 2) and II (with βblocker,n = 2). Comparing renal function through CrCL, statistical differences ($p<0.01$) allowed us to create groups III (CrCL = 157.06±36.27mL/min,n = 2) and IV (CrCL = 68.91±4.14mL/min,n = 7). However, so far, no significant differences in terms of DIG PK parameters were detected between GI and GII (GI:AUC_{0-24} = 19.40±1,73ng.h/mL,C_{max} = 1.10±0,08ng/mL, T_{max} = 5.00±3,00h;CL/F = 0.187±0,088L/h/kg X GII:AUC_{0-24} = 22.16±7,26ng.h/mL,C_{max} = 1.26±0,13ng/mL, T_{max} = 1.50±0,50h;CL/F = 0.102±0,045L/h/kg) nor GIII and GIV (GIII: AUC_{0-24h} = 28.83±4.57ng.h/mL, C_{max} = 1.63±0.41ng/mL, T_{max} = 1.00±0.00h,CL/F = 0.088±0.026L/h/kg X GIV:AUC_{0-24} = 23.55±3.99ng.h/mL, C_{max} = 1.32±0.20ng/mL,T_{max} = 2.32±0.98h;CL/F = 0.139±0.035L/h/kg). **Discussion:** At first we allocated patients receiving DIG different doses in the same stratum because no significant difference was observed in terms of DIG PK due to the dosage (data not shown). Despite of our preliminary data, it is not possible to allege that carvedilol nor renal failure do not alter DIG PK because few observations were performed. Studies using volunteers showed influence of carvedilol and renal failure on DIG PK (Baris *et al*. Eur J Clin Pharmacol 62:535, 2006; Pereira. J Bras Nefrol 30(1):6, 2008). Patients' recruitment continues to enlarge each stratum sampling and allow an accurate evaluation of renal disease and carvedilol association influence on DIG PK. **Financial Support:** FAPERJ, CAPES, Proppi/UFF

11.006 Evaluation of subchronic toxicity of tyramine in rats. Morais TMF[1], Rodrigues HG[1], Dantas MB[1], Damasceno DV[1], Freitas AMP[1], Meneses RRC[1], Sousa DF[2], Oliveira GP[1], Oliveira KS[1], Queiroz MGR[1] [1]UFC – Análises Clínicas e Toxicológicas, [2]UFC – Fisiologia e Farmacologia

Introduction: Substances of natural origin are frequently used as raw materials for drug synthesis, as well for preparation of homemade medicines. Tyramine, an amine isolated from the leaves of S*olanum campaniforme*, has been shown to present preclinical pharmacological action on reduction of serum glucose levels in alloxan-induced diabetic rats and possible lipid-lowering activity. Despite these promising pharmacological activities, there are few studies about the safety of the long-term use of this substance. Therefore, the aim of this study was to evaluate the repeated dose toxicity in rats treated daily with tyramine for 28 days. **Methods:** All experimental procedures were approved by the UFC Ethics Committee for Animal Research under protocol number 24/10 and followed the guideline OECD 407 (1995). Wistar rats were treated daily with fresh water (NC) or tyramine doses of 10 mg / kg (T10), 20 mg / kg (T20) or 40 mg / kg (T40). Body weight, feed intake and water of all groups were measured weekly and the possible occurrence of toxic effects was monitored. After 28 days of daily treatment, the animals were deprived of food for 8 hours and had blood collected for hematological assessment (erythrogram, leukogram and platelet count) and biochemical parameters (glucose, triglycerides, cholesterol, total protein, albumin, AST, ALT, LDH, GGT, alkaline phosphatase, uric acid, urea and creatinine). After collection, the animals were sacrificed for analysis of macroscopic organs. **Results and Discussion:** Analysis by ANOVA and Tukey post-test ($p<0.05$) showed that the lowest dose of tyramine did not cause changes in the parameters studied. Despite glucose levels were increased in T20 (119.7±6.07 mg/dL vs. CN: 98.8 ± 3.34 mg/dL) and T40 groups (122.3±3.11 mg/dL vs CN: 98.8±3.34mg/dL), the animals remained physiologically normal, without evidence of any other typical signal of glycemic disregulation (ESPINOSA, Eur J Med Chem, 46: 2243, 2011). For GGT, an increase was observed in T20 (49.42 ± 3.75 U/L vs CN: 31.39 ± 4.40 U/L) and T40 groups (49.84±6.41 U/L versus CN: 31.39±4.40 U/L). Similar to other drugs, tyramine may promote enzyme induction without necessarily cause liver damage. Urea, a marker of renal function, was increased only in T40 group (46.50 ± 1.33 mg/dL vs 37.30±1.06 mg/dL). However, this parameter is considered limited by the fact that there are changes triggered by non-renal factors (OSTERMANN, Nephrol Dial Transplant 0: 1, 2012). Thus, our findings suggest that tyramine does not exhibit toxic effects for the period and concentrations tested. **Support**: FUNCAP, Capes

11.007 Toxicity of *Tropaeolum majus* L. in critical periods of pregnancy in Wistar rats. Lourenço ELB[1], Muller JC[2], Boareto AC[2], Gomes C[2], Lourenço AC, Minatovicz B[2], Gasparotto Junior A[3], Martino-Andrade AJ[4], Dalsenter PR[2] [1]Unipar/UFPR – Farmácia/Farmacologia, [2]UFPR – Farmacologia, [3]Unipar – Ciência Animal, [4]UFPR – Fisiologia

Introduction: *Tropaeolum majus* L. (Tropaeolaceae) is a native plant of the Andes in South America and it is widely distributed around the world. In Brazil, it is popularly known as"chaguinha", "capuchinha" and "nastúrcio". It has been used by the population for treatment of several conditions, including inflammatory processes, edema and genitourinary tract infections. In addition, recent publishing data shown that *T. majus* extracts posses hypotensive and anti-hypertensive effects through of angiotensin converting enzyme (ACE) inhibition (Gasparotto Junior *et al*; 2011). The aim of present study was to investigate the effects of *Tropaeolum majus* during critical periods of pregnancy in Wistar rats. **Methods**: Pregnant Wistar rats (±90 days old) were treated orally with hydroethanolic extract of *Tropaeloum majus* (HETM) at doses of 3, 30 and 300 mg/kg and reproductive assessment in the pre-implantation (from day 1° to 7° of gestation) and post-implantation (from day 8° to 20° of gestation) were investigated. At the end of each period of gestation the rats were euthanized and evaluated the following reproductive parameters. Pre-implantation period: number of corpora lutea and implants, absolute and relative weight of the uterus, ovaries, kidneys and adrenals and serum estradiol and progesterone levels. Post-implantation period: absolute and relative weights of liver and uterus, litter size, fetal weights, number of viable fetus, number of resorptions and histological parameters of the kidneys of fetus were evaluated as score: absent (-), discrete 1-5 (+), moderate 6-10 (++) evident > 10 (+++). All procedures were approved by the Institutional Ethics Committee of UFPR (authorization number 389). **Results**: In pre–implantation period were observed significant pre-implant losses (Control 9.74±2.41; HETM 3 23.59**±4.85; HETM 30 20.24*±5.91 and HETM 300 21.44*±5.17) and increased levels of estradiol (pg/ml) (Control 6.73±1.08; HETM 3 10.36±1.73; HETM 30 15.31*±1.99; HETM 300 16.67*±1.84) in all treatments when compared with the control group. In post-implantation period were observed a significant reduction in fetal weight (g) in males and females (20 days of birth) (males: control 3.42±0.02; HETM 3 3.39±0.02; HETM 30 3.24***±0.02 and HETM 300 3.27**±0.03; females: control 3.20±0.03; HETM 3 3.22±0.02; HETM 30 3.09±0.03 and HETM 300 3.06*±0.03). Kidney histological analysis showed dilated tubules (control (-), HETM 3 (+), HETM 30 (++) and HETM 300 (++)) and cysts in glomerular tufts (control (-), HETM 3 (+), HETM 30 (+) and HETM 300 (+)). **Discussion:** The toxic effects of hydroethanolic extract of *Tropaeolum majus* (HETM) during the pre-implantation may be associated with increased levels of estradiol. Furthermore, the observed changes in fetal weights and renal morphology observed in post-implantation period are due to a possible reduction in the levels of angiotensin II that has an important role in proto-oncogenes activation and renal maturation. **References:** Gasparotto Junior, A. *et al.* J. Ethnopharmacol. 134: 363, 2011. **Financial support**: DEGPP/UNIPAR, CAPES

11.008 Molecular profile of the men1 gene in multiple endocrine neoplasia type 1, clinical aspects and response to the pharmacological treatment: A case study.

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Introduction: The Multiple Endocrine Neoplasia (MEN) are complex syndromes characterized by the occurrence of tumours involving two or more endocrine glands within a single patient. The MEN1 is a rare autosomal dominantly inherited syndrome with an estimated prevalence of 1 to 10 per 100.000 individuals. It is caused by a mutation that inactivates the *MEN1* gene (tumor suppressor gene). The clinical manifestation of MEN1 is defined by the associated occurrence of at least two of the three main endocrine tumors related to MEN1: primary hyperparathyroidism (PHP), pituitary adenoma (PA) and gastroenteropancreatic tumors (GEPs). The PHP is the most common and the first clinical manifestation of MEN-1 in more than 85% of all patients, whereas the PA may be the first one in about 25% of sporadic cases. This study aims to describe the clinical aspects and the response to the pharmacological treatment of a MEN-1 patient, correlating with the mutational profile of the *MEN1* gene. **Methods:** This study was approved by the ethics committee of the Federal University of Ceará, COMEPE n. 192/11. Four milliliters of peripheral blood were collected for DNA extraction using the QIAamp DNA Blood Mini Kit from QIAGEN®. All the coding region of the *MEN1* gene was amplified by the Polymerase Chain Reaction (PCR). PCR products were purified and standard protocols were used for cycle sequencing. Sequences were determined after capillary electrophoresis and analyzed using the software CondonCode Aligner®, in order to draw a mutational profile. The index case was a patient with initial diagnosis of PA (prolactin-secreting), who after 09 years of follow-up was diagnosed with PHP. Due the diagnosis of MEN-1, the patient was subjected to an abdominal tomography, which showed a nodular lesion with exophytic component in the pancreas (28x28mm anterosuperior surface of body). Biochemical testing for secretory GEPs were normal. **Results and Discussion:** The patient underwent surgery (body-tail pancreatectomy+splenectomy+left gastric artery lymphadenectomy+subtotal parathyroidectomy implanting the lower right parathyroid in the left forearm+thymectomy). The histopathology confirmed pancreatic endocrine neoplasia (56x36x23mm) with malignancy characteristics (>2cm angioinvasion) and presence of angiolymphatic infiltration. Immunohistochemistry showed Ki67 of 18%, indicating further treatment with chemotherapy. The response to the pharmacological treatment (chemotherapy: etoposide and cisplatine, four cycles) was satisfactory, without relapse until now. Through the screening of the *MEN1* gene it was possible to report two germline mutations (heterozygous), one in exon 3 (c.669G>A) and another at the beginning of exon 5 (c.801G>A). No mutations were observed in the other exons. However, it was not possible to set a genotype-phenotype correlation, which agrees with several previous studies on MEN1 families. Further studies are already in development with 34 MEN-1 patients (8 families) in order to assess whether it is possible a genotype-phenotype correlation, including the response to the pharmacological treatment, when a larger population is analyzed. **Supported by:** CNPq, CAPES, FUNCAP and PRONEX.

11.009 Canrenoic potassium reduces contractile response in non vascular smooth muscle. da Silva Neto JA[1], Wanderley AG[2], Miranda-Ferreira R[1], Caricatti-Neto A[1], Jurkiewicz A[1], Jurkiewicz NH[1] [1]Unifesp – Farmacologia, [2]UFPE – Farmacologia

Introduction: Canrenoic potassium is a derivated from metabolism of spironolactone. Is used in parenteral administration and its action as an antimineralcorticoid with a potassium-sparing diuresis is applied in cases of congestive heart failure and hypertension, therefore its acute actions still did not clearly elucided. The aim of this work was to evaluate the acute effects of canrenoic acid potassium - CAP (3 mM and 5 mM) in a model of non-vascular smooth muscle. **Methods:** *Rattus novergicus albinus* was kept in the cage with food and water ad libitum and 12h light/dark cycle. The animals were killed by decapitation and the vas deferens carefully removed and mounted in organ bath with modified Tyrode's solution (33°C). The CAP was incubated for 30 minutes before the assays. The contraction values were expressed in contraction force (grams/grams of tissue) with Emax ± SEM in each experiment performed with n = 5. **Results and Discussion:** CAP reduced the values on concentration-response curves by constrictor agents, such as adrenergic agonist Phenylephrine (Phe = 36,56 ± 1,7 and Phe + CAP 5 mM = 18,86 ± 2,4; $P < 0,05$), noradrenaline (NA = 37,20 ± 1,5 and NA + CAP 5 mM = 27,43 ± 1,9; $P < 0,05$) and cholinergic agonist carbachol (Cch = 23,10 ± 1,75 and Cch + CAP = 13,91 ± 1,94; $P < 0,05$). In depolarized condition CAP reduced the contractile effect of $CaCl_2$ (Ca^{2+} = 30,12 ± 1,84 and Ca^{2+} + CAP = 21,40 ± 1,57; $P < 0,05$) but In presence of tetraetilamonium (0,1 mM), a potassium channels blocker, CAP was attenuated the reduction of contractile response. In tetraetilamonium-induced tonus (10 mM), CAP was able to totality avoid the tetraetilamonium-induced contraction. After the depolarizing effect by KCl (80 mM) CAP reduced phasic and tonic contraction. In neurogenic contraction by electrical stimulation (50V 3 ms) CAP was reduced contraction in frequencies of 2, 5 and 10 Hz. These results suggest that CAP reduced the effect of various the agents used for contractile responses by hyperpolarizing phenomena. **Financial Support:** CAPES, CNPq and FAPESP.

11.010 Design, synthesis and evaluation of novel inhibitors of focal adhesion kinase (FAK) for cardiac hypertrophy, fibrosis and cancer. Antunes JE[1], Cardoso L[2], Pereira MBM[2], Dalla APC[2], Clemente CFMZ[3], Rocha RO[3], Franchi Jr GC[4], Rocco SA[3], Franchini KG[3] [1]Unicamp – Farmacologia, [2]Unicamp – Fisiopatologia Médica, [3]LNBIO-CNPEM, [4]Unicamp – CIPOI

Introduction*:* FAK is a non-receptor protein tyrosine kinase that accumulates at focal adhesions where it has been assigned a central role in integrin adhesive signaling[i]. FAK is implicated in the regulation of many biological processes, such as on cell proliferation, migration and survival[ii]. Furthermore, the development of malignancy is often associated with perturbations in these processes; it is not surprising that FAK activity is altered in cancer cells. Studies showing that FAK expression is increased in human tumors make FAK a potentially important new therapeutic target[iii]. There is evidence for involvement of FAK in cardiac remodeling from experimental and human studies[iv]. There is a high correlation between the degree of hypertrophy and FAK expression during the transition from compensatory left ventricular hypertrophy to heart failure. **Methods***:* The methods used in this work were: computational tools, organic synthesis; medicinal chemistry tools; Kinase Assay *in vitro;* Western blotting; MTT; pharmacokinetics parameters by HPLC; Mass Spectrometry; Aortic Coarctation; Masson Trichrome for fibrosis, transgenic mice specific for FAK where techniques were used to cardiac histology and echocardiogram grafting. **Results***:* We have developed news inhibitors of FAK, through of computational tools and medicinal chemistry. It was obtain the 4BZLO that inhibited the *in vitro* activity of FAK in 50% with 1nM. Among the pharmacokinetics parameters obtained, the $t_{1/2}$ was approximately 17 hours and hasn't seen toxicity in animal models. The *in vivo* study was used to evaluate the response of new drug in animal model of cardiac fibrosis. The results showed that animals treated with the drug during 15 and 30 days presented as reduced accumulation of collagen as controls. The license number Animal Ethics Committees is 2186-1 (CEMIB-UNICAMP). Our laboratory has developed transgenic mice specific for FAK that develops moderate cardiac hypertrophy. These transgenic animals were treated with the new drug to evaluate the reduction of cardiac hypertrophy. The treated group showed a reduction of the size, diameter of heart and improves cardiac parameters. The 4BZLO was tested for cell viability of 24 different types of neoplasms which we used the MTT method. In two trials (solid tumors and leukemia cells), the 4BZLO showed better results when compared to the reference drugs, which include doxorubicin and vincristine. **Discussion***:* FAK silencing markedly attenuated the interstitial fibrosis, strengthening the notion that FAK plays a critical role in the myocardial fibrogenesis induced by chronic pressure overload. Furthermore, the expression and activity of FAK is increased by several types of cancer such as breast, acute myeloid leukemia, neuroblastoma, etc.[v], thus the results obtained with 4BZLO shows that it is a promising new drug. **Acknowledgments:** FAPESP that is financial agencies and National Laboratory Bioscience (LNBIO). [i]Kornberg L, *et al*. *J Biol Chem* 267: 23439,1992. [ii]Cox BD, *et al.*. *J Cell Biochem* 99: 35,2006. [iii]McLean, G.W. *et al. Nature Rev. Canc.*5: 505,2005. [iv]Lopes MM, *et al.Clin Sci (Lond)* 113: 195,2007. [v]Golubovskaya, V.M., *Anticancer Agents Med Chem*. 10: 735,2010.

11.011 Evaluation on the effectiveness of gel of aroeira (*Myracrodruon urundeuva*) in the process of cicatrisation in mice. Seabra FT, Câncio KS, Laurentino MR, Costa LL, Marques KF, Ferreira JR, Alves RS UFC – Clinical and Toxicological Analysis

Introduction: Cicatrisation is the name given to the repair process, which is done at the expense of the proliferation of fibrous tissue. The growing interest in Phytotherapy by the scientific community in the last two decades has led to the development of various searches based on common practices. The *Aroeira (Myracrodruon urundeuva)* is a plant of the Brazilian territory known for its healing properties so that it is very popularly used in the treatment of wounds in general. **Methods:** We evaluated the cicatrisation effect of topical administration of the aqueous gel of *aroeira* in open wounds in the dorsocostalis region of mice. We used 10 adult male mice with circular lesions on the dorso made with punch with of 6mm diameter. The animals were divided into two groups: control group (n = 4), treated with gel without any active ingredient**,** and the treated group (n = 6), treated with gel containing the *aroeira* (0,1mg/g). Each group was subdivided into two subgroups to be observed at 7 and 14 days. The lesions were treated once a day, 24 hours after the induction of wounds, by applying approximately 2 mg of the respective gels. At each application, we measured the size of lesions (Approved by the animal ethics committee of the Federal University of Ceará: protocol 25/12). **Results:** Macroscopically there was an improvement in cicatrisation in all groups. Measurements of the size of the lesions were not accurate in that the tail of the animals was not photographed, thus their identification was compromised. In microscopy, the plate were stained with HE and analyzed by optical microscopy, which assigned numerical values for the following items: the crust of fibrin (0 = absent, 1 = present); reepithelialization (0 = absent, 1 = mild, 2 = moderate, 3 = severe) inflammatory infiltrate (0 = absent, 1 = mild, 2 = moderate, 3 = intense), angiogenesis (0 = absent, 1 = mild, 2 = moderate, 3 = severe); collagen deposition (0 = absent, 1 = mild, 2 = moderate, 3 = severe); population of fibroblasts (0 = absent, 1 = mild, 2 = moderate, 3 = severe), and necrotic areas (1 = absent, 0 = present .) After the analysis, the group that received treatment for 7 days with *aroeira* obtained a general average of nine points, whereas the group that received treatment for 14 days achieved an overall average of 1. In this group we observed full reconstitution of the skin. The control group was only assessed at the end of 14 days, and the overall average points scored by this group were 3.75. **Discussion:** On day 14, macroscopically, there was no great variation between groups is possible to identify a full re-epithelialization and hair growth. However, microscopy showed a significant difference between control group and the group treated with *aroeira*. Since this is a preliminary work, we used a smaller sample size, a factor that, initially, could compromise the results. We intend to repeat the experiment by raising the "n" groups, and from that develop the study of diabetic animals. **Keywords**: Aroeira gel; Wounds; Healing. **References:** White Neto, M. L. C., Evaluation of hydroalcoholic (Schinus terebinthifolius Raddi) in the process of wound healing in rat skin. Acta Brazilian Surgery - Vol 21 (Supplement 2), 2006.

11.012 Comparison of antifungal activity of imidazoles and triazoles against strains of *Candida albicans*. Câncio KS, Castro IN, Menezes EA, Oliveira MCS, Cunha FA UFC – Clinical and Toxicological Analysis

Introduction: Invasive fungal infections (IFIs) remain a cause of morbidity and mortality among high-risk patients. *Candida albicans*is the yeast most commonly isolated of IFIs, an opportunistic pathogen that can cause disseminated infections in specific patient groups. The main drugs used to fight fungal infections is the azoles, these are divided into imidazoles and triazoles. Azole antifungals, inhibit lanosterol 14-ademethylase (CYP51), which is an enzyme that catalyzes the final step in the synthesis of ergosterol, an important component of the fungal cell membrane. The azole antifungals are divided: imidazoles, which contain two nitrogen atoms, and the triazoles containing three atoms. The antifungal susceptibility testing is a notable advance in the treatment of fungal infections and is the primary tool to establish suitable antifungal therapy. Comparison of antifungal activity may help in establishing the treatment of patients with fungal infection. **Methods:** The objective of this study was to evaluate antifungal effect of imidazoles (ketoconazole, clotrimazole and miconazole) and triazoles (fluconazole, itraconazole and voriconazole) against *Candida albicans*. We studied 30 strains of *C. albicans. Candida albicans* strains were obtained from inpatients at Hospital Geral, Fortaleza, which were from different anatomical sites (urine, respiratory tract and blood). The strains were identified by the germ tube test, chlamydospore production and assimilation tests. The susceptibility of *C. albicans* isolates to imidazoles and triazoles was tested using the broth microdilution assay as described in the CLSI document M27-A3. **Results:** All 30 strains tested were sensitive to antifungals tested. However fluconazole showed the greatest minimum inhibitory concentration (MIC) among antifungal triazoles, showing that its prophylactic use has led to the emergence of resistant strains, voriconazole and itraconazole had the lowest MIC. The miconazole, clotrimazole and ketoconazole showed an important antifungal activity. However, miconazole showed the lowest activity group of the imidazole. **Discussion:** This work shows that *Candida albicans* remains sensitive for antifungal imidazoles and triazoles. **Keywords**: *Candida albicans*. Imidazoles. Triazoles. **References:** Boelaert, J.;. Miconazole plasma levels in healthy subjects and in patients with impaired renal function. Chemotherapy, v.6, p.165-169, 1976. Brajtburg, J.; Amphotericin B: delivery systems.Antimicrob Agents Chemother, v.34, n.2, p.381-384, Feb. 1990.

11.013 Assessment of the embryotoxic effect of LASSBio 596, a new antiasthmatic prototype designed by structural modification on thalidomide, on embryos of Zebrafish. Berto-Júnior C[1], Guimarães JPD[1], Soares RA[1], Barbosa LMC[1], Costa ML[2], Barreiro EJ[1], Lima LM[1], Souza AM[1] [1]LASSBio-FF-UFRJ, [2]ICB-UFRJ

Introduction: Thalidomide, an anti-inflammatory, sedative, immunomodulatory and antiangiogenic drug was originally developed in the 1950s to treat morning sickness associated with pregnancy. In 1960 the incidence of congenital anomalies, characterized by shortened limbs of newborns were found. Despite the toxic effects, this molecule retains good pharmacological properties, and was approved in 1998 for the treatment of erythema nodosum leprosy, by the ability to inhibit the TNF-α synthesis. Aiming to separate the good pharmacological profile of thalidomide from its toxicological activities, some molecular modifications were introduced in thalidomide structure resulting in the design and synthesis of LASSBio-596. This compound planned by molecular hybridization between thalidomide and aryl sulfonamides was synthesized and its anti-inflammatory activities determined, showing outstanding anti-inflammatory activity in murine models of asthma (LIMA, Bioorg. Med Chem, v. 10, 3067, 2002). Since 1975, the Food and Drug Administration (FDA) classifies drugs according their teratogenic risk. In respect to asthma treatment there is no drug in category A (studies proving no risk to the fetus), some are in category B (no evidence of risk in humans) and the vast majority are of the category C (risk cannot be discarded), reflecting the absence of studies in this area. Considering the former observation and the structural similarity of LASSBio 596 and thalidomide, determining the teratogenic potential of new bioactive compounds with potential antiasthmatic effect and the identification of the molecular mechanisms involved in this process constitute the crucial steps in the planning, development and optimization of this prototype.
Methods: Zebrafish embryos were alocated on a six well plate and incubated with LASSBio-596, thalidomide, salbutamol, ASA or vehicle, in indicated concentrations, and allowed to growth for 72 hours. The phenotype analysis was peformed at 24, 48 and 72hpf. When indicated, chorions were removed by gentle enzymatic degradation with 2mg/mL Pronase E solution for 1 minute. All procedures were performed as described in the “Principles of Laboratory Care” (NIH 85-23, 1985) and approved by Animal Ethics Committee (protocol DAHEICB 012). **Results**: In a concentration-response experiment, with LASSBio 596 concentrations ranging from 0,1 to 400mM, we could observe the following results: 1) at higher concentrations LASSBio 596 (100 mM-400mM) the totality of zebrafish embryos die, whereas no mortality effect was observed in the presence of thalidomide 400 mM or lower concentrations of LASSBio 596 (1-50mM), when compared with the control; 2) The morphological analysis of 72 hpf zebrafish larvae, previously (2hpf) exposed to treatment with lower LASSBio 596 concentrations (1-50mM), indicate the same malformations of otical vesicle and pectoral fin development that was observed for thalidomide 400mM, with variable severity of the phenotype. Some drugs with no described teratogenic effects, like salbutamol and AAS, do not showed teratogenicity in this model. **Discussion**: Taken together these data point to a teratogenic effect of LASSBio-596 probably by a similar pathway observed to thalidomide. However it remains to be determinate the exact molecular mechanism and the structure-activity relationship correlated to such effect.
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11.014 CYP2C19 variability in a group of volunteers of Goiás State, **Brazil**. Silveira KSA[1], Teixeira LSA[1], Filgueira FP[1], Mendonça HRS[2], Castelli EC[3], Ghedini PC[1] [1]UFG – Farmacologia e Fisiologia, [2]UFG – Neurologia e Psiquiatria, [3]UFG – Genética Humana

Introduction: The *CYP2C19* gene presents variation sites that may affect the pharmacokinetics of several drugs of clinical importance, including antidepressant medications. Their polymorphism gives rise to important inter-individual and inter-ethnic variability regarding the metabolism of therapeutic agents and may cause differences in clinical responses. The aim of this study was to evaluate the general variability of the CYP2C19 locus, focusing into three important alleles: CYP2C19*1, CYP2C19*2 and CYP2C19*3. These alleles were determined in a group of volunteers born in the state of Goiás, Brazil. **Methods**: All experiments were approved by the local Ethics in Research Committee (Protocol CEP/UFG 204/2009). The polymorphisms of CYP2C19 was evaluated by PCR-RFLP, defining the alleles CYP2C19*1, *2 and *3. DNA was extracted from blood samples obtained from 76 volunteers (46 males and 30 females, aged 19-50 years). **Results and Discussion**: Three genotypes were found in the present sample, including 58 subjects (77.6%) with no mutated alleles (*1/*1; homozygous extensive metabolizers, EM), 13 (17.2%) with one mutated allele (2 with *1/*2 and 11 with *1/*3; heterozygous EM), 4 (5.2%) with two mutated alleles (3 with*2/*2 and 1 with *3/*3; poor metabolizers, PM). Interestingly, no sample was found carrying two CYP2C19 mutated alleles (*2/*3) in the present series. We have provided preliminary results about the genetic analyses of the metabolizer status of *CYP2C19* gene in the population of healthy volunteers. In addition to these data, patient group and phenotype investigations are needed, since this information together might be used in provision of average dose recommendations of medications for different genetic subpopulations. **Financial Support**: FAPEG, CAPES, CNPq

11.015 Adenosine A2A receptor antagonists are broad facilitators of antinicotinic neuromuscular blockade monitored either with 2-Hz train-of-four or 50-Hz tetanic stimuli. Pereira MW[1], Correia-de-Sá P[2], Alves-do-Prado W[1] [1]UEM – Pharmacology and Therapeutic, [2]IBSAS-University of Porto

Introduction: The TOF_{ratio} is clinically used to monitor the degree of curarization in patient. Uncertainty about the usefulness of the TOF_{ratio} to control safe recovery from curarization prompted us to investigate the muscarinic and adenosine neuromodulation of tetanic fade induced by antinicotinic agents at concentrations causing a 25% reduction in the TOF_{ratio}. **Methods:** The Ethics Committee for Experimental Studies of the State University of Maringá approved the procedures (043-2007). The neuromuscular preparations of male Wistar rats (250g) were assembled according to Bülbring (Br J Pharmacol.; (1):38, 1946) and were indirectly stimulated at 0.2 Hz for 15 min. The phrenic nerve was stimulated with TOF stimuli and the muscular tension produced at the beginning of each train (T_1) was compared with the muscular tension obtained at the end the train (T_4). The TOF_{ratio} is the quotient of these two values (T_4/T_1) and was taken as a measure of drug-induced neuromuscular transmission failure (TOF_{fade}). To investigate the tetanic fade, the preparations were indirectly stimulated with four high-frequency (50-Hz) tetanic trains of 10 s duration that were applied at 15 min intervals. Initial tetanic tension at the beginning (A) and the tension at the end of the tetanic stimulus (B) were recorded, and the ratio ($FADE_{ratio}$) B/A was calculated. Four antinicotinic agents were evaluated in the present study d-tubocurarine, hexamethonium, pancuronium, and cisatracurium. The concentrations that consistently produced approximately 25% TOF_{fade} were determined and used to investigate the effects of the antinicotinic on the fading of tetanic contractions. The antinicotinic drugs were tested in the absence or presence of the presynaptic antagonists (10nM pirenzepine, 1µM methoctramine, 2.5nM DPCPX and 10nM ZM 241385). **Results:** Tetanic fade caused by D-tubocurarine (1.1 µM, 61.00±6.0%, *n* = 6), pancuronium (3.0 µM, 37.5±2.0%, *n* = 6), and hexamethonium (5.47mM, 88.0±1.0%, *n* = 6) were attenuated by methoctramine M_2 receptor blockade (5.0±1.8, 21.0±1.5, 59.3±5.7%, *n* = 6) and DPCPX A_1 receptor blockade (8.8±4.1, 23.0±2.8, 61.0±6.0%, *n* = 6), respectively. Similar to the observations with muscarinic M_1 and M_2 receptor blockade, DPCPX (2.5 nM) increased fade caused by 2.2 µM cisatracurium (from 17.30 ± 3.00% to 40.50 ± 4.50%, *n* = 6). Pretreatment with adenosine A_{2A} receptor antagonist, ZM 241385, attenuated tetanic fade produced by 1.1 mM d-tubocurarine (from 61.00 ± 6.00% to 0.80 ± 2.60%, *n* = 6) and 3.0 µM pancuronium (from 37.50 ± 2.00% to 18.00 ± 1.00%, *n* = 6). The ZM 241385, was the only compound tested in this study that prevented tetanic fade induced by 2.2 µM cisatracurium (from 17.30 ± 3.00% to 0.00 ± 0.00%, *n* = 6) **Conclusion**: The data suggest that distinct antinicotinic relaxants interfere with fine-tuning neuromuscular adaptations to motor nerve stimulation patterns via presynaptic muscarinic and adenosine receptor activation. These results support the use of A_{2A} receptor antagonists together with atropine to facilitate recovery from antinicotinic neuromuscular blockade. Sources of research support: Araucaria Foundation and FADEC-UEM.

11.016 Effects of LASSBio-788, **a potential antiatherogenic compound**, **on the male rat reproductive tract**. Alfradique VAP[1], Fernandes WO[1], Motta NAV[1], Kümmerle AE[2], Barreiro EJ[2], Brito FCF[1], Marostica E[1] [1]LAFE-UFF Physiology and Pharmacology, [2]LASSBio-UFRJ

Introduction: Atherosclerosis is closely associated with inflammatory and immune responses, besides to promote the activation of platelet aggregation and increase of oxidative stress. The development of drugs that combine anti-inflammatory, antiplatelet, antioxidant and lipid lowering properties are important for the treatment of this pathological condition. The compound LASSBio-788 is a thienyacylhhydrazone derivative that has a potencial antiatherogenic effect with antiplatelet, anti-inflammatory, vasodilatory, anti-oxidants and lipidic lowering *in vitro*properties (Brito et al, Eur. J. Pharmacol, 5, 2010; Motta, 2011). For this reason it is considered a potential candidate drug for the treatment of atherosclerosis. Therefore, it is important to evaluate the toxic effects caused by the drug on the tissues, such as the reproductive tract. Thus, the aim of this study is evaluate the possible toxicological effects in the rats testis treated with LASBio-788. **Methods:** 12 male Wistar rats (150-200g) (CEPA/UFF 0116/09) were separated in four groups (n = 3/group): CO-fed with commercial ration; AT-fed with hypercholesterolemic diet; AT+788 - fed with hypercholesterolemic diet, treated with LASSBio-788 (100µmol/kg ip) for 15 days; AT+L-fed with hypercholesterolemic diet, treated with cilostazol (100µmol/kg, ip) for 15 days. After 45 days of experiment, the animals were anesthetized and testes from different experimental groups were removed, weighed and processed for paraffin embedding. Sections of 5 mm were obtained and stained with hematoxylin/eosin for light microscopy. The area and diameter of 40 seminiferous tubules for each rat was measured using the program-NIS Elements Advanced Research and the mean of 3 animals in each group was determined. In addition, spermatogenic lineage cells (spermatogonia, spermatocyte and round spermatid) and Sertoli cells of these samples were also counted. From these scores, we obtained the Sertoli cell index (SCI = round spermatids/Sertoli cells) (França et al, J. Androl, p 335, 1998) of cross section of the seminiferous tubule. **RESULTS:** The values are mean±SEM. The results showed no significant variation between the experimental groups in the values found for diameter (CO:247.41±1.48, AT:248.37±2.63; AT+788: 267.14±1.82, AT+CL: 262.15±2.89 m) or tubular area (CO: 48628.24±572.73; AT: 49264.58±1058.81; AT+788: 56816.69±747.89; AT+CL: 1148.40±55076.384 m^2). In addition, no significant difference was observed in the count of spermatogonia (CO: 27.96±0.52, AT:27.36±0.58, AT 788: 25.17±0.54, AT+CL: 27.38±0.44), spermatocytes (CO:42.99±1.23, AT: 44.08±1.07), AT+788: 42.46±1.14, AT+CL: 40.02±0.52) and round spermatids (CO: 88.34±2.02, AT: 85.80±1.88; AT+788: 83.06±1.59; AT+CL: 87.09±1.44). For the Sertoli cells were obtained the following results: CO:14.52±0.39; AT:14.21±0.30; AT+788: 13.72±0.28; AT+CL (15.54±0.32) and the SCI (CO: 5.762±0.10; AT: 5.710±0.11; AT+788: 5.763±0.12; AT+CL: 5.326±0.096.) was not also different among the groups. **Discussion:** Our preliminary results showed that administration of LASSBio-788, a potential anti-atherogenic compound, did not cause any harmful effect on the spermatogenic process and testicular parenchyma structure and does not affect the functional efficiency of Sertoli cells in male Wistar rats. **Supported by:**CAPES, CNPq, FAPERJ.

11.017 Evaluation of the acute toxicity of proteolitics extracts with industrial potential in Wistar rats. Gomes LA[1], Silva TA[2], Liborio ST[3], Teixeira LO[3], Teixeira MFS[2], Moroni FT[4] [1]UFAM – Curso de Biotecnologia, [2]DPUA-UFAM, [3]Uninorte – Nutrição, [4]UFAM – Biotério Central

Introduction: The big food industries are increasingly expanding the search for natural biomolecules with potential for applications in processes or steps production. In this context, the fungal species and plants stand out in the biomolecules' production with potential for industrial application. According to ANVISA (National Health Surveillance Agency), for the inclusion of a new additive/food in products supporting marketed it is necessary that the new product will pass through a series of toxicologic evaluating including acute toxicity testing on laboratory animals that verifies the possible risks to human health. The objective of this study was to evaluate the effects of acute toxicity of six bioextracts with a proven potential of application in the food industry, through the oral administration in Wistar rats. **Methods:** It were used 42 Wistar rats, young adults, male and female, with average weight of 233.22 ± 41.83g, they were divided into 7 groups of females (n = 3) and 7 groups of males (n = 3). After seven days of acclimatization, the animals were treated orally (gavage) with single doses of freeze-dried extracts (4 extracts of filamentous fungi anamorphs, a native tree latex extract and an extract of edible mushroom badidioma) prepared in a concentration of 1000 $mg.kg^{-1}$, the group control received only water. The clinical evaluation has been carried out on animals for a period of 14 days. Signs of toxicity were measured by direct observation and registered in a table within the ranges 0, 15, 30 and 60 minutes and each period of 4 hours (during 24h) and daily until the 14° day. The body mass gain and feed intake also were registered on a daily basis for monitoring the evolution of animals by weight. At the end of the experiment, the animals were anaesthetized for deep analgesic and it was held the laparotomy for abdominal cavity longitudinal to collect blood of the animals via cardiac puncture, followed by an evaluation of macroscopic morphology of external organs. The obtained data were statistically analyzed by ANOVA and Tukey test. This work was approved by the Ethics Committee at animal use of UFAM, 2011/054 protocol. **Results and Discussion:** The administration of the extracts in a concentration of 1000 $mg.kg^{-1}$ did not result in death in any of the animals but also didn't cause significant behavioral changes. It also didn't interfered on the mass development, feed intake, as well as macroscopic changes in the viscera (liver and kidneys) weren't produced on the animals. The non-occurrence of death or of significant toxic signs in the animals treated indicated that the bioextracts evaluated in this research when administrated at dose of $1000mg.kg^{-1}$ in Wistar rats (males and females) have low or absence of acute toxicity in the conditions of the experiment. And therefore, it represents a great potential for use as a food additive. **Financially support:** CNPq and FAPEAM