Journal homepage: http: www.journalamb.com/index.php/jamb

The II International Symposium on Medicinal Chemistry and Regenerative Medicine, held from November 22nd to 24th at, this event was directed to undergraduate and graduate students, professionals from the medical, pharmaceutical, biotechnology innovation management and entrepreneurs, as well as researchers involved in the areas of Medicinal Chemistry, Regenerative Medicine and Biotechnology.

The event aimed to promote the dissemination of new research and innovations that are at the frontier of knowledge in the area of Regenerative Medicine and Medicinal Chemistry and also to promote interaction with companies interested in these researches. Thus, as a result of the event, it is hoped to encourage discussion, sharing of knowledge, articulation of partnerships for new research projects and also generate a spark of ideas that can be led by future entrepreneurs.

In this second edition, a scientific session was held with the presentation of posters. The abstracts submitted and approved by the scientific committee are below.

Central themes

- Biopolymers
- Medicinal Chemistry
- Regenerative Medicine
- Innovation Management on Biotechnology

Biopolymers - Abstracts

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Luminescent chitosan/sodium tripolyphosphate nanoparticles modified with [Eu(TTA)3(Bpy-si)] complex as new biomarkers

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ARTICLE INFO

Keywords:
Chitosan/sodium tripolyphosphate
nanoparticles
Silylated Europium(III) complex
Luminescent biomarkers

ABSTRACT

Introduction and objectives: Chitosan (CS) is a versatile, biocompatible, non-toxic biopolymer extremely abundant in the biomass obtained by alkaline deacetylation of chitin, easily found in the exoskeleton of crustaceans, and in some types of fungi and marine squid. CS has been widely studied by the pharmaceutical industry as a potential agent for the healing of bones and tissues, in treatments for weight reduction and cholesterol, as antimicrobial agent and suitable matrix for coordination compounds as lanthanides ions aiming applications such as cell markers. In this way, the development of new coordination luminophores non-toxic and stable with good luminescence properties even in small concentrations is still a big challenge. In this work, we described the ionic gelation technique as method to obtain Chitosan/TPP nanoparticles (CS/TPP) modified with luminescent silylated [Eu(TTA)3(Bpy-Si)] complex. **Materials and Methods:** All nanoparticles were prepared by ionic crosslinking of CS dispersions with TPP aqueous solutions, according to the ionic gelation method. The CS solutions were prepared by dispersion of 30 mg of CS in 10mL of acetic acid solution 0.1M at room temperature and mechanical stirring. NaOH aqueous solution 1M was used to increase the pH up to 4.4. After that, TPP solution (10 mg TPP in 10 mL of water) was added dropwise to 10 ml of CS dispersion under stirring at room temperature for 1h. Simultaneously, 3 mg of [Eu(TTA)3(Bpy-Si)] complex were dissolved in 3 mL of water and added dropwise to CS/TPP solution under stirring at room temperature for 1h. Finally, the CS/TPP@[Eu(TTA)3Bpy-Si] obtained was dialyzed for 48h. **Results:** The nanohybrids were characterized by FTIR, SS-NMR and FE-SEM techniques that confirm the incorporation of the [Eu(TTA)3Bpy-Si] showing particles with average size of 84 nm. Luminescent properties were evaluated and the intensity parameters were calculated. These results showed that after luminophor grafting onto nanoparticles there was no significant decrease in its luminescent properties indicating that chitosan/TPP nanoparticles can be used as a good biomatrix. The luminescent nanohybrids suspension was evaluated in B16F10 cells strain by epifluorescence microscopy. By excitation at 470 nm, red emission of these nanosystems in the cell nuclei can be observed. **Conclusions:** Preparation of CS nanoparticles and CS@[Eu(TTA)3Bpy-Si] were successfully performed and confirmed by FTIR, SS-NMR, FE-SEM and luminescent measurements. The complex incorporation into the biomatrix was not affected by the acid pH of the CS nanoparticles. The choice of the CS as biomatrix appearing is a good choice to maintain the luminescent properties of the complex. CS@[Eu(TTA)3Bpy-Si] as new biomarkers was confirmed by Epifluorescence microscopy in melanoma cells showing red emission in cell nucleus region.

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Orodispersible films based on gellan gum and cashew gum intended for insulin administration: evaluation of transparency and erosion

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ARTICLE INFO

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Cashew gum and gellan gum

ABSTRACT

Introduction: Orodispersible films (FOD) are intended for administration of drugs into the oral cavity. These films can be developed from polymeric materials, such as cashew gum (GC) and gellan gum (GG), since these materials show high mucoadhesive properties and rapid disintegration when placed in the oral environment. The development of these GG / GC-based FODs is in agreement with the need for an alternative route for the treatment of *Diabetes melittus*, since the subcutaneous route of insulin (INS) administration is an invasive route, causing discomfort, pain and local inflammation, decreasing patient adherence to treatment. The administration of INS through the FOD overcomes the drawbacks related to the enzymatic degradation of INS in the gastrointestinal tract, as well as its low intestinal permeability. **Objectives**: To analyze the degree of transparency of GG / GC FODs and its disintegration in artificial saliva. **Materials and Methods:** Polymeric films were obtained by the solvent casting method from GG: GC dispersions obtained in different proportions (1:2,5, 1:5, 2,5:2,5 and 2,5:1) and labeled as 1G / 2.5C, 1G / 5C , 2.5G / 2.5C and 2.5G / 1C, respectively. The FOD transparency measurements were performed on a Varian Cary 500 UV-Vis spectrometer at 200-800 nm interval. For the erosion test the FOD were cut and accurately weighed and then placed on the bottom of beakers containing artificial saliva solution at 37 ° C with 50 rpm stirring for 30 minutes. After the immersion time, the films were removed, oven dried at 60°C for 48 hours and weighed. Erosion was calculated gravimetrically. **Results:** The transparency measures in the visible region of the spectrum revealed that the films presented transmittance percentage ranging from 60 to 70%. The spectra showed that films that had a higher CG concentration had a lower transparency, which was attributed to the fact of GC did not completely disperse, blocking the passage of light. Likewise, films with a lower CG concentration had greater transparency as a consequence of a lower restriction on the passage of light. In the erosion test performed in simulated saliva solution, the 1G / 2.5C sample presented a lower percentage of erosion (19%), which is probably related to the higher concentration of GC, and it could be observed that in the 2.5G / 1C sample had a higher percentage of erosion (56%), with a lower GC concentration. **Conclusion:** We conclude that the degree of transparency of the FOD is a promising property, since it is a transparent solution and favors an application of the material in the biomedical area. According to erosion data, the 2.5G / 1C sample was more appropriate to use the FOD, since it presented a higher percentage of erosion in artificial saliva solution. Erosion testing is extremely important, since erosion also leads to a faster release of the incorporated drug, for mucoadhesive systems may be a good strategy for increasing permeation.

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Antimicrobial biomaterial based on polysaccharide

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ARTICLE INFO

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Gum
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ABSTRACT

Introduction: The manufacture and use of biodegradable biomembranes from polymer with incorporation of bioactive drugs or molecules has aroused industry interest for the manufacture of dressings used in wounds and sutures. Among these polymers, polysaccharides like gums stand out because of the property of forming films or membranes. However, these polysaccharides are water-soluble and need to have improved physical properties for such an application. **Objectives:** With the current challenge of developing new biodegradable matrices for drug incorporation, this work has the objective of making membrane for application as an antimicrobial dressing. **Materials and Methods:** Three types of modified polymer were developed and characterized by FTIR, elemental analyses. **Results:** Characterization by FTIR showed a presence of bands between 1560 and 1490 cm^{-1}, characteristics of amines functional groups. In addition, the modified gum exhibits anti-staphylococcal activity.

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Assessment of mutagenicity of polymer films of Allium Cepa L. With application for food packaging

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ARTICLE INFO

Keywords:
Food packaging
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Ames test

ABSTRACT

Introduction: Nowadays, most of the food packaging systems are based on petroleum-derived synthetic plastics, whose production has increased exponentially over the past two decades. Nevertheless, the utilization of these materials involves a serious environmental problem and high recycling costs. In order to deal with this issue, current research focuses on the development of biodegradable materials from renewable sources. So, polymer films of *Allium cepa* L. are being produced for this purpose. However, because it touches the food and chemicals can migrate into the food, their safety should be regulated. **Objectives:** Thus, the aim of the present study was to determine the mutagenic effects of the onion-based washed and not washed films (*Allium cepa* L.) with application for food packaging. **Materials and Methods:** The films were produced in BioSmart Nanotechnology Company and gently donated by Dr. Diógenes dos Santos Dias. Mutagenic activity was evaluated by the *Salmonella*/microsome assay (Ames test), using the *Salmonella typhimurium* tester strains TA98 and TA97a (detect frameshift mutations), TA100 (detect base-pair-substitution mutations) and TA102 (normally used to detect mutagens that cause oxidative damage and base-pair-substitution mutations), with (+S9) and without (–S9) metabolization, by the preincubation method. **Results:** The results showed only signs of mutagenicity of the not washed films with the largest mutagenic indexes of 1.9. The washed films did not induce an increase in the number of revertant colonies relative to the negative control, indicating absence of mutagenic activity, under the conditions used. **Conclusion:** The detection of genotoxicity is highly advisable, so as to avoid the risk of genotoxic exposure to mutagens and carcinogens. These results contribute to valuable data on the safe use these materials for commercial purposes. However, further investigations exploiting mutagenesis mechanisms should be conducted.

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Citotoxicity and mutagenicity studies of tempo-oxidized cellulose nanofibers

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ARTICLE INFO

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Biomaterials
Cellulose
Nanofibrillar cellulose
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Cytotoxicity

ABSTRACT

Introduction: Nanocellulose is described as a product or extract of a native cellulose composing a material with a nanomeric structure. Despite being considered the most attractive renewable material for advanced applications due to its unique physical and mechanical properties, little is known about the mutagenic potential and cytotoxic effects of nanoscale cellulose. Thus, the evaluation of mutagenicity and cytotoxicity in substances with promising applicability within tissue engineering, such as cellulose, is necessary owing to the fact that further tissue damages can be avoided. **Objectives:** Therefore, the objective of this study was to evaluate the mutagenic activity of TEMPO-oxidized cellulose nanofibers (ToCNF) by the Ames test, a widely used assay to detect mutations at the gene level, and its cytotoxic potential by the MTT assay. **Materials and Methods:** ToCNF was produced in UNIARA's BioPolMat laboratory and gently donated by Prof. Eliane Trovatti, PhD. In this study, the Ames test was performed with changed strains of *Salmonella typhimurium* (TA98, TA97a, TA100 and TA102) and for the MTT assay were employed a normal cell line (GM-07492) and a cell line with metabolism profile of carcinogens (HepG2). **Results:** According with the results obtained in this report, the modified cellulose did not induce any statistically significant difference neither in the number of revertant colonies of *S. typhimurium* nor of the cell viability when compared to their respective negative controls in both experiments. **Conclusion:** The absence of mutagenicity and cytotoxicity is extremely relevant because it provides reliable data to support future clinical researches. However, further toxicological tests are needed to ensure its safe use.

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Rheological behavior of sodium alginate hydrogel containing bacterial cellulose

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ARTICLE INFO

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Bacterial cellulose
Hydrogel
Sodium alginate
Rheology

ABSTRACT

Introduction and objectives: Hydrogels are three-dimensional hydrophilic networks with capable of absorbing large quantities of water or biological fluids. Hydrogels are biodegradable and biocompatible with long-term stability, ease of biochemical modifications of formed structures, and enables the incorporation of organic/inorganic products. Various polymeric materials are used to form hydrogels; however, the use of polysaccharides, such as the use of alginate hydrogels has been increased due to the biocompatibility, biodegradability, immunogenicity, and non-toxicity properties. The possibility of incorporation of bacterial cellulose (BC) nanofibers into alginate hydrogels is very interesting in several areas of knowledge, such as medicine, since the structure of BC is a viable matrix to assist the treatment of dermal lesions and it has been used as a temporary substitute for skin, burns, ulcers, grafts, as a wound cover and to aid in dermal abrasions. The aim of this work was to develop alginate hydrogels containing BC nanofibers and also investigate the rheological behavior of the developed hydrogels which impact when applied to the skin. **Materials and Methods:** Hydrogels of sodium alginate with calcium were developed using different polymeric materials and also it was incorporated different concentrations (0.5% and 1% in relation to the dry mass) of BC. Rheological behavior was evaluated with parallel plate rheometer (Anton Paar) was used to measure the complex viscosity (η*) the storage modulus (G') and the loss modulus (G") as a function of frequency. Tests used 25mm diameter plates at a temperature of 32°C. The range of frequencies used was 0.01 to 500 rad/s^{1}at 2%strain, which proved to be in the linear viscoelastic range according to a prior amplitude sweep test. The gap between plates was 1.00 mm. Flow curve was also analyzed with shear rate range from 0 to 100Pa / s for the ascent ramp for 120 seconds and from 100 to 0Pa /s for the descent ramp for 120 seconds. **Results and Conclusions:** The results obtained in this study demonstrate that alginate hydrogels with CB presented a thixotropic behavior, facilitating the application of the product under the skin with a pleasant sensorial. Results of the and frequencys weep shows that Alginate/BC hydrogels has adequate interaction among the components indicating a stable structure which makes it difficult to separate the constituents of the formulation besides being indicative of greater stability of these hydrogels.

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Cytotoxicity, antimicrobial activity and morphology of bacterial cellulose with chitosanfilm loaded with ciprofloxacin

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ARTICLE INFO

Keywords:
Bacterial cellulose
Chitosan
Wound healing

ABSTRACT

Introduction and objectives: Treatment of skin lesions is a great clinical importance, justifying the high investments in new products that reduce the time of healing and increase the patient comfort. As a result, different products and patches are market, however, most are imported and make the treatment expensive. In this context, biopolymers gain prominence in the industry due to its efficient, abundant and low cost, such as bacterial cellulose and chitosan. In the present work, the objective was to analyze the cytotoxicity, antimicrobial property and morphology of the film produced by bacterial cellulose and chitosan associated with ciprofloxacin. **Materials and Methods:** Cytotoxicity assay was performed by the MTT reduction method ({3- (4,5-dimethylthiazol-2-yl) -2,5-diphenyltetrazolium bromide), which allows measuring the amount of viable cells based on the principle reduction of MTT salt by mitochondrial enzymes to formazan (ISO 10993-5), in human fibroblast cells GM07492.Inhibition halos against *Pseudomonas aeruginosa* and *Staphylococcus aureus* were determined by using modified disk diffusion method according to international clinical standards (CLSI/NCCLS), replacing disks for empty and ciprofloxacin loaded BC/chitosan films in the agar plate surface (Mueller Hinton agar) and inoculated with bacteria (0.5 McFarland scale). SEM experiments were carried out using samples previously coated with evaporated carbon. The images were obtained using the JEOL T-300 microscope operating at 2 kV. **Results:** Cytotoxicity assay demonstrated that the negative control group and CB determined the same pattern of cell viability, evidencing the absence of toxicity from the extract of the CB membranes analyzed. Ciprofloxacin loaded BC/chitosan samples exhibited a significant but slight decrease in the metabolic activity of cells. In contrast, it does not characterize a cytotoxic influence, considering the percentage of viability exhibited in the analyzes (greater than 80%).Antimicrobial activity tests, the ciprofloxacin loaded BC/chitosan film demonstrated activity for both bacteria tested, in evidence against *Pseudomonas aeruginosa* that showed higher activity than against *Staphylococcus aureus*. The results also showed the antimicrobial activity of chitosan against *Pseudomonas aeruginosa*, evidenced in the small inhibition halo formed when inoculated the BC/chitosan film, without ciprofloxacin. Analysis of SEM images revealed surface and transversal section morphology of films. The surface was homogeneous and characteristic of chitosan. From the transversal sectional images, was observed the chitosan in the center of film immersed in the bacterial cellulose membrane, and at the extremities of the film. **Conclusions:** Generally, the film did not prove to be toxic, in addition, it presented antimicrobial activity against the tested microorganisms and had its morphological structure characterized. Presented research work will open new prospect for the development of composites that could be used as wound dressing and them potential applications in tissue engineering.

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Effect of palygorskite clay on the release properties of metronidazole from bacterial cellulose membranes

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ABSTRACT

Introduction and objectives: Bacterial cellulose (BC) is synthesized by different species of bacteria and shows many advantages in relation to plant cellulose. In pharmaceutical field, BC has been successfully exploited in the design of controlled drug delivery systems due to its well-organized 3D network of fibers. Although the highly porous structure of BC can be used successfully for the preparation of new nanocomposites, it promotes the fast release of the drug in a short time (burst release), which can cause the side and toxic effects, constituting a pharmacologically dangerous and economically inefficient. In order to overcome this drawback, the aim of this work was to explore the high adsorptive capacity of paligorskite (PAL) due to the high density of silanol groups on the external surface and high internal area as a strategy for the effective entrapment of the metronidazole (MTZ). PAL is a natural clay that presents fibrous morphology with 2:1 crystalline structure. **Materials and Methods:** PAL was dispersed in an aqueous MTZ solution (10 mg/mL) in different proportions (1:1, 7:1 and 15:1) under magnetic stirring at 750 rpm, 30 °C for 72 h. BC membranes synthesized by *Komagataeibacter rhaeticus* in Hestrin and Schramm culture medium were allowed to swell in PAL-MTZ solutions until complete absorption. *In vitro* MTZ release was carried out using USP type V dissolution apparatus (paddle over disk) in a Hanson Research (New Hanson SR-8 Plus) dissolution station, using phosphate buffer (0.1M; pH 6.0) according to sink conditions, at 37 ± 0.5 °C under 50 rpm rotation speed. **Results:** Release profiles showed that MTZ directly incorporated in BC (0 % PAL) depicted a burst effect of release (62%) in the first 30 min, which is probably attributed to the high porosity of BC, as well as to the drug molecules adsorbed on the membrane surface, allowing their free diffusion. After 180 min of test, 82 % of MTZ was released. Samples containing 1:1 and 7:1 PAL:MTZ were not effective in the release control, showing a release profile similar to that of the control sample. However, the sample prepared with the highest ratio of PAL (15:1) allowed the prolongation of release rates, so that after 180 min of test, only 60 % MTZ was released. According to the kinetic study, the mathematical model that best correlated was that of Weibull, with parameter b>1, revealing that the MTZ release was governed by a complex mechanism, involving diffusion, swelling and erosion. **Conclusion:** The set of results indicate that the strategy proposed to overcome the fast release of drugs from BC matrices was very efficient, suggesting its use as an important technological platform for controlled release.

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Hybrid bacterial cellulose - pectin films for transdermal delivery of bioactive molecules

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Bacterial cellulose
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Antimicrobial patch
Polymeric film
Levofloxacin

ABSTRACT

Introduction and objectives: Novel biopolymeric films based on bacterial cellulose (BC) modified with high methoxylated pectin (HMP) were developed for transdermal drug delivery. **Materials and Methods**: The ability of films to incorporate an antibiotic, levofloxacin (Levo), was analyzed. Incorporation efficiencies (EE) were determined using films with different proportions of HMP (from 0.1% to 2.0%) with a maximum drug payload of 6.23 mg/g. **Results:** Characterization studies revealed the existence of a cooperative network between both polymers and deep structural changes in BC matrix. Besides, HMP presence decreased water loss in the BC film from 93% to 75% after 90 min. Additionally, film incorporation capacity of macromolecules, using Human Serum Albumin (HSA) as a model protein, was studied. HMP presence enhanced in more than 3.5 times the EE of HSA and no pH dependence was observed. Release kinetics of both molecules showed hyperbolic profiles with sustained release. On independent experiments, HMP presence generated around 50% decrease on both macromolecules release rates. Additionally, the incorporation of HSA into BC-HMP matrix exhibitied a modulation on Levo release profile. The antimicrobial activity of Levo released from the BC-HMP-HSA films was confirmed using *Staphylococcus aureus*. In-vitro studies revealed no apparent cytotoxicity of the released compounds in mammalian CHO cells. **Conclusion:** As a conclusion, on this work the versatility of bacterial cellulose material was tested by *in situ* modification with an additive biopoolymer. The hybrid material exhibited proper characteristic for its application as a transdermal graft with antibiotic properties.

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Biocomposites based on tpp crosslinked chitosan / bacterial cellulose as a potential strategy for Ciprofloxacin release

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ARTICLE INFO

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Acterial cellulose
Chitosan
Ciprofloxacin

ABSTRACT

Introduction and Objectives: Bacterial cellulose (BC) presents high crystallinity, fibers of nanometric size gives it a greater water hold capacity and not contain lignin, pectin and hemicellulose in its structure. The polymer has been studied, produced and applied in several areas. Chitosan is a polysaccharide obtained from the N-deacetylation of chitin, consisting of polymeric (1→4)-linked 2-amino-2-deoxy-β-D-glucopyranose units. Because of the biocompatibility, non-toxicity, biodegradability, and intrinsic antibacterial properties, chitosan is considered as a versatile material with potential biomedical applications. Therefore, the aim of this work was to use bacterial cellulose crosslinked with sodium tripolyphosphate (TPP) and chitosan loaded with ciprofloxacin and to evaluate the antimicrobial capacity and the in vitro release study of ciprofloxacin. **Materials and Methods:** The commercial kitLIVE / DEAD BacLight® were used for microbiological assays and the bacteria *Pseudomonas aeruginosa* and *Staphylococcus. aureus* were incubated at 24 hours to allow biofilm formation. Subsequently, biofilms were completely covered with empty and ciprofloxacin loaded BC/Chitosan films for 10, 30 and 60 min. Controls with untreated bacteria (Live) and HClO treated biofilm (Dead) were performed. Then, were observed in a Leica DM 2500 epifluorescence microscope (Germany) equipped with UV filters (495–505 nm) at 400X to determine the viability of the bacteria. Ciprofloxacin release was evaluated in phosphate buffer (10.0mM pH 5,8). Briefly, one film (10 mm) was incubated in 20 mL buffer at 37°C. Samples were taken at different times, and ciprofloxacin was measured at the maximum absorbance wavelength (277 nm). **Results**: For both *Pseudomonas aeruginosa* and *Staphylococcus. aureus*, a reduction in the bacterial population was observed after 30 and 60 minutes of contact with the bacteria, increasing as time passed. The release profile of ciprofloxacin showed a gradual release in 15 min (37%) and 25 min (52%) until a burst in 50 min (80%) and follow constant. After this quickly release, significant percentages of the amounts of drug released up to 300 min were not observed, suggesting a prolongation of the release, which could be exploited for pathologies in which an initial loading dose is required, followed by maintenance of the dose of the antibiotic. **Conclusions:** The rapid release verified by the study suggests that the system provides an enough drug for its effectiveness, corroborating with the antimicrobial activity test.

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Synthesis, pressing and characterization of bacterial cellulose produced by *Komagataeibacter Rhaeticus*

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Hydraulic Press
Central Composite Design

ABSTRACT

Introduction and Objectives: Cellulose is a homopolymer of D-glucopyranose residues linked by β-(1 →4) glycosidic linkages and is metabolized in plants, animals and secreted by specific genera of bacteria. Bacterial cellulose (BC), presents high crystallinity, fibers of nanometric size which gives it a greater water hold capacity and differs from vegetal cellulose as it does not contain lignin, pectin and hemicellulose in its structure. The polymer has been studied, produced and applied in several areas. However, about BC produced by *Komagataeibacter rhaeticus*, there are few reports in the literature regarding its characteristics, either after a process of membrane pressing. Therefore, the objective of this work is the characterization of the morphological structure and mechanical and thermal characteristics of the BC after pressing process of hydraulic press and drying. **Materials and Methods:** After being purified, the membranes were pressed by a hydraulic press, evaluating the variables: pressing time of 10, 20 and 30 seconds and forces of 1, 2 and 3 tons, according to central composite design to verify the influence of the press in parameter morphological, mechanical and thermal.SEM experiments were carried out using samples previously coated with evaporated carbon. The images were obtained using the JEOL T-300 microscope operating at 2 kV. Mechanical properties of membranes were evaluated using texture analyzer TA-XT2 (Stable Micro Systems). Force displacement curves were recorded until the film rupture and used to determine the puncture strength (Ps), elongation at break (Eb), perforation energy (Ep). Thermogravimetric analyses were performed using an SDT Q600 (TA Instruments, USA), at 20 °C/min under nitrogen atmosphere (30 mL/min). **Results:** SEM images shows that the pressed samples presented more compacted fibers, and tended to align in the same direction as the increase of the force and time of pressing. It was also observed a lower porosity when compared to CB without treatment. In the mechanical analysis, BC with treatment presented a progressive puncture strength, according to a gradual increase of force and pressing time, however, this value was lower with BC without treatment. In the elongation at break, BC without treatment presented lower value when compared to the membranes with treatment that presented greater elongation. All samples showed a similar thermal behavior, the curves obtained displayed two mass losses. The first one, a small mass loss related to loss of surface water (~ 3.7 - 5.5). The second mass loss event was attributed to the sample decomposition process of cellulose (~74 - 84 %). **Conclusions:** The data obtained so far show that the use of the BC treatment press can change its morphological structure beyond the mechanical and thermal properties.

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Babassu Mesocarp (*Orbignya phalerata*) Modified With Phthalic Anhydride For Applications In Electrochemical Sensors Of 5-Fluorouracil Chemotherapeutic

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ARTICLE INFO

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ABSTRACT

Introduction and Objectives: 5-Fluorouracil (5-FU) is a broad-spectrum drug used in the treatment of neoplasms such as glioblastoma and several other cancers, including head and neck cancer, gastrointestinal tract cancer, and breast cancer. On the other hand, there is no knowledge of a level of exposure to 5-FU that is considered safe, for example, for those who are not in chemotherapy treatment. The occupational exposure to 5-FU, even for a short time, as is the case of healthcare professionals who administer these drugs, can cause adverse effects such as skin rashes, nausea, hair loss, allergic reactions, damage in DNA, etc. Thus, it is very important to develop low-cost sensors capable of detecting 5-FU in different samples and at low concentrations. In this perspective, the objective of this study was the development of electrochemical sensors for detection of 5-FU, from the use of a polymer extracted from babassu mesocarp (BM), which was chemically modified with phthalic anhydride (BMPA) to improve its solubility and electrochemical properties. **Material and Methods:** The reaction for BMPA synthesis was based on literature. A flexible gold electrode (FEAu) was constructed for this study, in which the cost of the electrode was estimated at approximately 0.027 US dollars. The FEAu was modified with a micro droplet (10 μL) of a solution containing BM or BMPA at 1.0 mg/L. The electrochemical assays were performed in a conventional electrochemical cell, using FEAu/BMPA as working electrode. **Results:** The modification in babassu mesocarp with phthalic anhydride was confirmed by FTIR, XRD, TG/DTG, Zeta Potential, and SEM analysis. The modification caused a very positive effect on the electrochemical behavior of the polymer, since the BMPA showed a more reversible redox process and with greater electrochemical stability in relation to BM. The current of oxidation process of 5-FU had an increase of 276% when FEAu/BMPA electrode was used. Also was observed a displacement in the oxidation potentials of BMPA in presence of 5-FU, suggesting strong interaction between them. After construction ofa calibration plot for 5-FU using FEAu/BMPA electrode, the analytical sensitivity and the limit of detection for 5-FU were estimated at 8.8 μA/μmol/L and 3.4×10^{-7} μmol/L, respectively. **Conclusions:** Electrochemical sensors developed from babassu mesocarp may be an economically viable alternative for monitoring of the 5-FU antineoplastic, since in addition to being sensitive to this drug they are constructed of a natural polymer, renewable and widely abundant in nature.

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Development of sensor device based on purified palygorskite associated with antimicrobial peptide DRS 01

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ARTICLE INFO

Keywords:
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Pithecopus hypochondrialis
Nanostructured Films
Layer-By-Layer

ABSTRACT

Introduction and Objectives: Biomolecules immobilization is a promising approach in development of sensor devices. Antimicrobial peptides (AMPs) are part of the innate immune system of several organisms with firmly established antibiotic potential that can be used as recognition elements for target substances in biosensor devices. Clay minerals are inorganic solids of crystalline structure with morphology and unique physicochemical features, such as adsorptive and thermal properties. In this sense, these inorganic systems have emerging as suitable matrices for anchorage of organic molecules. This work reports the purification, characterization and application of nanocrystals of palygorskite (PAL), a fibrous clay mineral from Guadalupe (state of Piauí), for immobilization of the peptide Dermaseptin 01 (DRS 01) bylayer-by-layer (LbL) technique to develop an electro active film for applications as biosensor device. **Materials and Methods:** The natural PAL was submitted to physical and chemical purification processes for the enrichment of its adsorptive properties and the concentration of clay-mineral. Structure, chemical composition and morphology of PAL were investigated by X-Ray Diffraction (XRD), Fourier-Transform Infrared spectroscopy (FTIR), X-Ray Fluorescence spectrometry (XRF), Scanning Electron Microscopy (SEM) and Transmission Electron Microscope (TEM). LbL films based on PAL and DRS 01 were prepared by alternating immersion of Indium tin oxide (ITO) substrates in dispersions of 1 mg/mL of PAL and DRS 01 for five minutes. Films were electrochemically characterized by Cyclic Voltammetry (CV) in 0.1 mol L^{-1}phosphate buffer (pH 7.25), UV-Visible spectroscopy, FTIR attenuated total reflection (FTIR-ATR) and Atomic Force Microscopy (AFM). **Results:** PAL was purified with enrichment of its properties as confirmed by XRD and FTIR techniques with pronounced reduction of quartz peaks. The results for ITO/DRS 01 and ITO/PAL/DRS 01 films showed an oxidation process at +0.77 V, confirming that DRS 01 maintained its electro active behavior, when together with PAL. The results of CV showed differences in the current density of 1.82 μA cm^{-2} for the film containing unpurified PAL (ITO/PAL-IN/DRS 01) to 2.63 μA cm^{-2} in the film containing purified PAL (ITO/PAL/DRS 01). The 3-bilayer ITO/$(PAL/DRS\ 01)_3$ film showed an increase in current density values that was around 4.60 μA cm^{-2} compared to the film with a single bilayer. **Conclusions:** The purification of clay mineral played an important role in the electrode response. The nanostructured film developed emerges as a low-cost platform, versatile and easy to prepare, even on other substrates, for biodetection of pathogens in clinical, environmental and pharmaceutical analysis, as well as other biotechnological applications.

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Scaffolds of pla (POLYLACTIC ACID) obtained by additive manufacturing functionalized with calcium polyphosphate coacervate for application in tissue engineering

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ARTICLE INFO

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Tissue Engineering
PLA
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Scaffolds

ABSTRACT

Introduction: Tissue Engineering have been gaining prominence, since it has a wide range of applications. The general purpose is development of biological substitutes for repairing and/or replacement of damaged tissues. There are three basic elements for tissue engineering: Cell, which is responsible for formation of new tissue; Biocompatible Polymer Matrix, which provides an appropriate environment and support for cell growth; and the Growth Factors, which are biologically active molecules that stimulate and define the cell differentiation. 3D printed poly-acid lactic scaffolds could be a promising technology for tissue engineering applications. In order to improve cell adhesion and proliferation on PLA scaffolds, 3D samples have been modified with polyphosphate coacervate, which is a rich gel-like containing mainly phosphorus and calcium elements. **Objectives:** The aiming of this work is surface modification of 3D-PLA scaffold using polyphosphate coacervate as coating and modifier agent. **Materials and Methods:** Commercial filaments of PLA were used to build 3D-scaffolds (10 mm of diameter and 5 mm of height) by UP-3D plus 3D printer. 3D-PLA scaffolds were submerged for 24 h in polyphosphate coacervate at room temperature. PLA-Coacervate samples were frozen and lyophilized. **Results:** SEM images indicate that the polyphosphate coacervate clusters were within PLA 3D structures. The layer-by-layer scaffold structure was kept intact. EDS data indicates presence of oxygen, phosphorus, sodium, chlorine and calcium, the main components of polyphosphate coacervate and PLA. Structural and thermal analyses confirmed that the coacervate polyphosphate was incorporated in PLA scaffolds. **Conclusions:** Cytotoxicity and cell adhesion preliminary tests suggest the possibility to use this new scaffold in medical applications.

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Filaments for 3d printing based on polymeric blends of poly-hydroxybutyrate / starch for applications in tissue engineering

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ABSTRACT

Currently have been growning the interest in biopolymers for the production of biomaterials using 3D printed, since they are biodegradable, biocompatible and non-toxic. Among all natural polymers, poly-hydroxybutyrate (PHB), which is a polymer produced from bacteria *Alcaligenes eutrophus*, it is a renewable, linear, semi-crystalline resources and belonging to the class of poly-hydroxyalkanoates. The main disadvantage of this biopolymer is the high cost in production and some deficiencies in their properties such as low mechanical resistance and thermal instability. To address these deficiencies is possible the association of PHB with natural additives, such as starch, cellulose and others natural polymers. In this work, polymers blends filaments based on different proportions of PHB/ starch have been prepared using a homemade extruder of single screw. The obtained filaments have been characterized as Scanning Electron Microscopy (SEM), thermogravimetric analysis (TGA), mechanical tests of tensile and impact, and biodegradation test. The filaments have also been tested using 3D printed fused deposition modeling (FDM) method in order to produce prototypes that can be applied as a biomaterial in tissue engineering.

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▷Innovation Management on - Abstracts

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Regulatory process of a bioceramic laboratory by the health surveillance guideliness

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ARTICLE INFO

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ABSTRACT

Introduction: Biomaterials production companies, specially, bone grafts based in bovine bone mineral matrix (CaP), needs approval and certification by the competent health organizations, in order to commercialize safely in the Brazilian market. Thereby, they depend on the guidelines and its complementary rules of the collegiate board of directors in the Nacional Health Surveillance Agency (ANVISA) and Health Ministry (MS) at national level; in a state level, the standards are secured by the State Secretary of Health (SES/SP) and municipal by the Health Surveillance (VISA). **Objectives:** The purpose of this abstract is to understand which are the regulatory standard to manage a laboratory. By them, develop all quality system (SQ) documents in accord to the internal processes of fabrication and operation. All these documents are necessary to have a Technical Authorization Report (LTA), allowing a company located in São Carlos/SP to commercialize its products. **Materials and Methods:** To do so, the SQ management must be written in accord on the guidelines of the collegiate board resolution (RDC) nº 16/2013 (Technical Regulation of good manufacturing practices for health products), RDC nº 02/2010 (Management of health technologies in health facilities) and RDC nº 306/2004 (Technical Regulation for the management of waste of health services). These are the main national guidelines and, using them as base; it was written (i) Manual of Good Fabricating Practices (BPF); (ii) the Standard Operating Procedures for Specific Processes (POP-PE), (iii) of Equipment (POP-EQ), (iv) and of Good Fabricating Practices (POP-BPF); (v) the Solid Waste Management Plan (PGRSS) and the Equipment Management Plan (PGE). **Results:** From these documents, a physical adaptation project of the company has been created to suit the pattern of sections, people, processes and raw material flow required by the VISA in the RDC nº 50/2002 (Technical Regulatory to plan, program, elaboration and evaluation of physical projects of health care establishment). All documents were filed to VISA and, in a preview analysis, it was opened the regulatory process. In the end of the physical reform, all the documents are going to be reviewed and the VISA will perform the audition of the regulatory process. With the LTA approved, different compositions of CaP will be produced and offered in the Brazilian market. **Conclusions:** The importance of this work was to solve an existing problem inside the company, and to report in a scientific base the regulatory process, so that future entrepreneurs can use this method.

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Towards an academic spin-offs maturity model

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ABSTRACT

The university has been challenged to include entrepreneurship inside the undergraduate and graduate programs, as a way to motivate new venture companies and innovation. This challenge is being faced by universities around the world. In Brazil, the teaching of entrepreneurship, in most institutions, follows the traditional method. This work aims to present an academic spin-offs maturity model, based on the model of Fiates et al. (2008), which is a representation of a business acceleration model. The Fiates model considers 5 fundamental factors to describe the spin-off maturity levels, which are: the entrepreneur, the product, the capital, the market and the management. The proposal of this research aims to incorporate new dimensions for Fiates' maturity model. The research project foresees a review of the spin-offs maturity models, cited in the literature, and case studies of academic spin-offs for the identification of new dimensions of spin-off maturity model. The proposal model will have validated from comparative analysis. The paper discuss how to organize the teaching of entrepreneurship, in order to meet all the maturity levels of the academic spin-off, combining theory and practice, from the prospecting and technological application. This project will generate practical results, such as actions to foster academic entrepreneurship and strengthen students' entrepreneurial training. In addition, the results can be to contributing in the field of entrepreneurial university theory.

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Regulatory process of a bioceramic laboratory by the health surveillance guideliness

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ARTICLE INFO

Keywords:
Regulatory Guidelines
Health Surveillance
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Introduction: Biomaterials production companies, specially, bone grafts based in bovine bone mineral matrix (CaP), needs approval and certification by the competent health organizations, in order to commercialize safely in the Brazilian market. Thereby, they depend on the guidelines and its complementary rules of the collegiate board of directors in the Nacional Health Surveillance Agency (ANVISA) and Health Ministry (MS) at national level; in a state level, the standards are secured by the State Secretary of Health (SES/SP) and municipal by the Health Surveillance (VISA). **Objectives:** The purpose of this abstract is to understand which are the regulatory standard to manage a laboratory. By them, develop all quality system (SQ) documents in accord to the internal processes of fabrication and operation. All these documents are necessary to have a Technical Authorization Report (LTA), allowing a company located in São Carlos/SP to commercialize its products. **Materials and Methods:** To do so, the SQ management must be written in accord on the guidelines of the collegiate board resolution (RDC) nº 16/2013 (Technical Regulation of good manufacturing practices for health products), RDC nº 02/2010 (Management of health technologies in health facilities) and RDC nº 306/2004 (Technical Regulation for the management of waste of health services). These are the main national guidelines and, using them as base; it was written (i) Manual of Good Fabricating Practices (BPF); (ii) the Standard Operating Procedures for Specific Processes (POP-PE), (iii) of Equipment (POP-EQ), (iv) and of Good Fabricating Practices (POP-BPF); (v) the Solid Waste Management Plan (PGRSS) and the Equipment Management Plan (PGE). **Results:** From these documents, a physical adaptation project of the company has been created to suit the pattern of sections, people, processes and raw material flow required by the VISA in the RDC nº 50/2002 (Technical Regulatory to plan, program, elaboration and evaluation of physical projects of health care establishment). All documents were filed to VISA and, in a preview analysis, it was opened the regulatory process. In the end of the physical reform, all the documents are going to be reviewed and the VISA will perform the audition of the regulatory process. With the LTA approved, different compositions of CaP will be produced and offered in the Brazilian market. **Conclusions:** The importance of this work was to solve an existing problem inside the company, and to report in a scientific base the regulatory process, so that future entrepreneurs can use this method.

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Technological forecasting on additive manufacturing for bone tissue engineering in Brazil

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ABSTRACT

Introduction: Biomaterials are biological or synthetic materials used as technologies that will interface with a biological system, with the aim of repairing tissues or compromised functions in the organism of humans and other animals. With the advent of 3D printers, biomaterials have reached better performance levels due to the possibility of producing parts on a small scale and using geometrical forms little used in the existing techniques. **Objectives:** The present study describes the beginning of a technological forecasting study on additive manufacturing used in bone tissue engineering in the Brazilian context. **Materials and Methods:** To this end, a search was made in the Web of Science database, using keyword combinations of three complementary topics: (i) bone tissue engineering, (ii) materials (in this case, as bone grafting is the main goal, calcium phosphates were used such as Hydroxyapatite) and (iii) additive manufacturing. The results were processed using the VantagePoint v. 5.0 software in order to carry out a bibliometric analysis of the records retrieved. **Results:** A total of 720 articles from 44 countries and 695 institutions were retrieved and analyzed. Regarding countries, the main agents in the scene of tridimensional printing in bone grafting are China (24.1%), the USA (20.8%) and Germany (13.6%), while Brazil is in 18th place, with 14 articles published (1.94%). In Brazil, the beginning of research into this technology was in 2008 at the State University of Campinas (UNICAMP - SP) and reached its peak in 2013 with 4 publications, and the Federal University of Rio Grande do Sul (UFRGS - RS) continues to be the main producer of knowledge. Of the 14 articles published in Brazil, 35.7% were with international participation from Belgium, Japan, Portugal, Spain, Switzerland, the USA, Germany and Italy. **Conclusions:** This data describes Brazil as not being influencing country on this technique. Furthermore, it has been shown to be an emerging process in countries that have an established tradition in technological production. It should be observed that, while the first studies of using 3D printing in bone grafting dates from the end of the 1980s, in Brazil, it only began 20 years later. Therefore, this study shows a delay in Brazil regarding this technology application. In order to gain more conclusions about this topic worldwide and in Brazil, other routes of datamining must be followed. This should be done in future work considering other databases, particularly in the areas of engineering and biomedicine, as well as using specific patent databases.

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Science awareness coffee: a contribution to the development of the entrepreneurial ecosystem with researchers from Araraquara / SP.

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ARTICLE INFO

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Entrepreneurial ecosystem

ABSTRACT

Introduction: Between 1987 and 2008 there was a growth of more than one thousand percent in the number of doctorate graduates in Brazil. However, in order to reach proportions similar to that of developed countries, a 4.5-fold increase in the participation of PhDs in their population would be necessary. On the other hand, there is an alarming fact: formation of cadres to meet the demands of the postgraduate degree itself no longer accounts for absorbing the picture formed. In 2007 and 2008, 39.8% of the recent doctors "did not were found as employees". In view of this state of affairs, an increasingly promising alternative is entrepreneurship, although what has been seen is that the higher the degree, the lower the level of entrepreneurship. It seems that undertaking is a synonym of abandoning the academic career, but in several centers of academic excellence, actions are being put into practice to bring the academy closer to the market: Leaders in innovation fellowships of the University of Oxford, Babson College and also the creation of several Science Parks in all the state of São Paulo. The process of creation of a company has a complex character and is linked to a set of social, cultural and economic factors.To raise the success rate of academic entrepreneurship activities it is necessary to establish motivation mechanisms for students with Entrepreneurship potential. Entrepreneurial capacity refers to a type of human capital that comprises the set of knowledge resources and skills, which are essential for an opportunity of achievement, combined with the motivation to do so. **Objectives:** Aiming at the development of low cost exploratory strategies to foster sustainable scientific entrepreneurship, we proposed a series of meetings called "ConsCiência Coffee" – or Science awareness Coffee. **Materials and Methods:** Researchers from the Araraquara/SP region meet monthly to choose and discuss topics of common interest to improve their entrepreneurship skills. Some of the questions include: "How much is my idea, innovation or company worth?"; "What is the best legal and tax aspect to initiate an enterprise", "What is the bureaucratic way to open a company?"," How can CANVAS structure and Business Plan be applied to each innovation?". **Conclusions:** Based on these questions, approaches have been promoted to various partners, such as CANVAS workshops and the construction of various public communication tools on academic entrepreneurship, projects and innovations, as well as the possibilities of new partnerships, expanding the local entrepreneurial ecosystem.

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Biomodulatory influence of low-intensity laser therapy and serum rich in growth factor inhuman fibroblasts cells

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Platelet-rich plasma
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ABSTRACT

Introduction: Low-intensity laser therapy (LILT) and serum rich in growth factor (SRGF) derived from the human platelet-rich plasma technique (hPRP) are clinically used as biostimulants agents in tissue repair. The use is justified by the ability to stimulate cell proliferation and differentiation, the synthesis of extracellular matrix components and local neoangiogenesis. On the other hand, the effectiveness of these techniques, as well as administration parameters, are not properly established. **Objectives:** Thus, the present study aimed to characterize, in an *in-vitro* condition, the biomodulatory influence of both techniques on human fibroblast cells. **Materials and Methods:** Samples of blood from a male volunteer were centrifuged for fractionation of platelet-rich plasma and activated with calcium chloride (10% m/v) to obtain SRGF. Human fibroblasts (line GM07492) were seeded in 24-well plates ($5x10^4$ cells) in DMEM culture medium supplemented with 2.5% SRGF or fetal bovine serum (FBS). The groups related to LILT evaluation were submitted to laser radiation at wavelengths (λ) of 685 and 830nm. Doses of 0.3, 0.6, 0.9, 1.2 and 1.5 J/cm² with power density of 18 mW/cm² were evaluated. The cell viability were determined by the MTT-Formazan colorimetric assay 24 hours after irradiation and expressed as percentage of viability of control group (DMEM+2.5% FBS). The results were established by descriptive statistical procedures and variance analysis (ANOVA), complemented by Fisher's post-test. **Results:** Comparison of cell viability between the group using FBS and SRGF showed no statistical differences, indicating similarity in the viability potential between the growth factors sources. Regarding LILT, both λ showed biomodulatory potential on human fibroblast viability, although the effective dose, type and intensity of modulation were significantly different. Radiation at λ 685 nm provided a 40% increase in viability at dose of 0.6 J/cm². The λ of 830 nm resulted in a 60% increase in viability at the dose of 0.3 J/cm² and a reduction of 15% and 10% at the doses of 0.9 and 1.2 J/cm², respectively. This biomodulatory influence was not modified by human PRP-derived growth factors. **Conclusions:** These results demonstrate a λ and dose-dependent biomedulatory potential of LILT on human fibroblasts in vitro, which was not influenced by the action of SRGF derived from hPRP technique.

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Low-level laser therapy increased the number of ovarian follicles in the polycysticovaries-induced rats

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ABSTRACT

Introduction: Rats induced to polycystic ovaries (PCO) present ovarian alterations in both folliculogenesis and steroidogenesis. There is a reduction in the number of follicle and corpora lutea in addition to appearance of folliclecysts. Hyperandrogenemia is a consequence of steroidogenic alterations which induces irregular estral cycles. Low-level laser therapy (LLLT) and Light emitting diodes (LEDs) therapies have been investigated and used in clinical practice related to biomodulating influences on cellular functions both *in vivo* and *in vivo*. **Objectives:** The objective of this study was to analyze the LLLT effects on the number of the ovarian follicles in PCO-laser treated rats. **Materials and Methods:** Forty-five female adult Wistar rats weighing 250g-300g were divided into control (n= 15), PCO (n= 15) and PCO/laser (n= 15). PCO rats were induced by injection of estradiol valerate (EV) (2 mg/kg/wb, i.m., one-step). After PCO induction rats were divided into 30, 45 and 60 days after injections. The animals were manually contained and irradiated with laser at the wavelength of 808nm, with power between 60 mW, in a dose of 3 Joules (J)/ point, for 18 seconds on the dorsal region, performing a transillumination on each ovary 3 times a week, totaling 6 J of energy per irradiated animal/per day of application. After sacrifice the ovaries were collected for preparation and subsequent analysis of the histological slides. The results are presented as mean ± SEM. Significant statistical differences among the means of the treatment groups were decided for p-values<0.05. This study was approved by local Animal Care and Use Committee (CEUA–UNIARA, protocol nº 019/16). The results are reported as the means ± SEM. **Results:** The results showed that the largest number of follicles was observed in the control group 30 days (8 ± 1) and the lowest number was observed in the PCO group 60 days (1.66 ± 0.57). The 60-day PCO/laser group (6.66 ± 0.57) presented a higher number of follicles compared to the PCO group and equal to the control group. **Conclusions:** The results allow us to conclude that the use of LLLT increased the number of ovarian follicles in the PCO-induced rats apparently restoring the ovarian activities of folliculogenesis.

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Resistance exercise can promote morfofunctional changes in ovary polycystic-induced rats

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ABSTRACT

Introduction: Polycystic ovary syndrome (PCOS) is a heterogeneous syndrome characterized by an ovulation, clinical and/or biochemical signs of hyperandrogenism and abnormal ovary morphology. Rats induced by polycystic ovary (PCO) presents structural and functional ovary modifications that compromise the estrous cycle. The induction of PCO in rats using Estradiol Valerate (EV) is an interesting model because it develops ovarian alterations similar to PCOS in women. **Objectives:** The objective of this study was to identify possible changes in body weight, ovarian weight, gonado somatic index (IGS) and maximal voluntary carrying capacity (MVCC) at the end of the training in PCO-induced rats submitted to resistance exercise. **Materials and Methods:** Forty female adult Wistar rats weighing 200g-300g were divided into 2 group: 30 days (n= 20) and 45 days (n= 20) after PCO induction, and these groups were divided into 4 sub-groups: control (n= 5), PCO (n= 5), control/training (n= 5) and PCO/training (n= 5). The PCO induction was performed with a single dose of EV (2 mg/ 0.2 mL/rati.m.). The resistance exercise chosen was stair climbing (3 times/week) with loads added to the tails of the rats. The data were analyzed using ANOVA and Tukey's test. Significant statistical differences among the means of the treatment groups were decided for p-values<0.05. This study was approved by local Animal Care and Use Committee (CEUA–UNIARA, protocol nº 025/16). **Results:** For the 30-day group: the left ovary weight was higher for the control group (0.09708 ± 0.015 g) compared to the PCO/training group (0.06904 ± 0.0123 g). For the 45 day group: the body weight of the control group (367.2 ± 18.3g) was greater than the PCO group (274.8 ± 18.47 g) and the PCO/training group (290.8 ± 20.52 g). The PCO/training group had a lower body weight than the control group. For the 45-day group: the right ovary weight of the control group (0.0584 ± 0.0129 g) was greater than the PCO group (0.0276 ± 0.0063 g). There was no statistical difference for either IGS or MVCC. **Conclusions:** The PCO-induced rats by EV is a viable model for studies that correlate ovarian and metabolic alterations. This PCO-induced model is compatible with metabolic and reproductive characteristics of human PCOS and can be used for the study of physical exercise intervention on endocrine-reproductive mechanisms. In addition, resistance exercise can modulate adaptations in the body and ovarian masses of PCO-induced rats.

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Development and evaluation of lamelar denso scaffold for tissue engineering

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ABSTRACT

Introduction: Acute myocardial infarction (IAM) continues being responsible for the reduction in life expectancy and large numbers of deaths worldwide. Tissue engineering for cardiac tissue regeneration has been an alternative to restore the structure and mechanical functionality of the heart. Scaffolds are porous three-dimensional support, temporary, used to mimic the structure of the extracellular matrix and stimulating specific cellular responses at the cellular level / molecular organic tissue for regeneration. **Objective**: To project, to development and to evaluate dense lamellar scaffolds with potential use in tissue engineering. **Materials and Method**: The hydrogels, for fabrication of scaffolds, were prepared by mixture of collagen, chitosan and Poloxamer 407. Scaffolds for AMI were produced by plastic compression (using hydrostatic press). Briefly, cast highly hydrated hydrogels were transferred to a porous support comprising (bottom to top) absorbent paper blot layers, a steel mesh and two nylon meshes. The matrices were freeze-dried, resulting in cross-linked collagen-chitosan scaffolds. The samples were evaluated by swelling efficiency, porosity, interconnectivity and pore size, Fourier transform infrared spectroscopy and physiomechanical properties. **Results**: The physical mechanism controlling solute uptake was observed as anomalous transport, with the n values equal 0.79. The scaffold showed high interconnectivity of the porous with 71.68% of the porosity. The pore dimensions estimated from SEM microphotographs for scaffold was in the range of 15 – 25 μm. The FTIR spectrum of the blend polymers shows the characteristic bands of the parent molecules. No additional bands were identified indicating that did not have chemical interaction between the polymers used in the formulation. The results of physiomechanical properties like as elasticity, flexibility, drilling, traction and mucoadhesion were 0.608 ± 0.044 N, 0.635 ± 0.029 N, 2.001 ± 0.022 N, 1.806 ± 0.058N and 0.648 ± 0.040 N, respectively. **Conclusion:** The lamellar scaffolds obtained by the blend of collagen and chitosan, by plastic compression, showed promising feature in the application of the tissue engineering.

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Characterization of collagen and evaluation of potential use as gel in tissue engineering

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ABSTRACT

Introduction: Collagen is the most abundant protein in the extracellular matrix and has been considered to be a group of proteins with a fibrillar structure, which contributes to the extracellular scaffolding. In the presence of acid, alkalis and saline aqueous solutions a considerable increase in the amount of water absorbed by the collagen is reported. The isoelectric point of the collagen is in the range of 6.5 to 8.5, and any deviation from this pH (i.e. change in the isoelectric point) may cause non-specific swelling. **Objective:** To investigate the difference between collagen fiber (CF) and powder (CP), in different pH, with potential use as biomaterials in tissue engineering. **Materials and Method**: The CF and CP characteristic were evaluated using differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR). The gels were obtained in different collagen concentration (0.50, 0.75 and 1.0 %) and mediums with pH 7, 4 and 2 (water, acetic acid and sodium phosphate, respectively).The gels were evaluated by water holding capacity (WHC) and gelation temperature (Tsol-gel) between 8-38°C. **Results:** Thermoanalytical curve showed three thermal transition, next to 85°C (loss of water and denaturation of collagen protein), 227°C and 275°C (degradation) for both samples (CF and CP). The chemical groups showed by CF and CP were compatible with literature. Collagen gel has Tsol-gel behavior at low temperatures, that is, with the increase in the temperature occurs the decrease of the gel viscosity, therefore, the gel collagen shows Tgel-sol (transition temperature gelled/solution). The average value for WHC of the CP and CF was 92% of initial mass of the gel. As concentration as medium were factors that influence the Tsol-gel of the gels. For gels containing 1% of collagen did not occur Tsol-gel, the preparation keep itself gelled in all temperatures. CF showed Tgel-sol at 23°C to 0.75% in water, 17°C to 0.5% in sodium phosphate medium and 33°C to 0.5% in acetic acid. CP in water showed Tgel-sol at 22°C and 31°C for 0.50% and 0.75%, respectively. CP in sodium phosphate showed Tgel-sol at 11°C and 21°C for 0.50% and 0.75%. In acetic acid medium the Tgel-sol was observed only to the 0.50% concentration of the CP. **Conclusion:** The medium used to prepare the CP and CF gels influenced significantly the Tgel-sol behavior. The concentration of CP or CF can be modulated in an attempt to achieve the Tgel-sol proper. The CP and CF gel shows potential use in tissue engineering as injectable gel and in the scaffold fabrication.

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PLA (polylactic acid) scaffold printed by 3d tecnology and functionalized by plasma of oxygen

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ABSTRACT

Introduction: The purpose of tissue engineering is to repair, replace, create or regenerate tissues and organs. Tissue engineering depends on a triad composed of cells, scaffolds or structures, polymers, and growth factors. Nowadays, it is necessary to use the biomaterial that allows tissue engineering to build and shape through 3D technology to support cells, repair organs with biocompatibility, and chemical and physical properties that allow the surface to work. Among the polymers, we can use PLA (polylactic acid). PLA has physical properties as well as biodegradability and biocompatibility. Thus, the PLA has characteristics necessary for the manufacture of a scaffold. The scaffold is a support or structure that allows there generation of tissues. To create a scaffold, we use rapid prototyping. This new field of research is a versatile technique for generating large quantities of shapes and sizes of polymers. Three-dimensional (3D) printing, also known as the manufacture of additives (AM), extrudes the polymeric material into layers. Rapid prototyping (RP) represents the direct manufacturing of pieces per layer, guided by digital information from a computer-aided design (CAD) file without any specific part tool. To promote and increase properties such as hydrophilicity, adhesion, and proliferation, on the surface of the scaffold, we must work the surface with oxygen plasma. **Objectives:** The goal of this study is to develop polylactic acid scaffolds printed by 3D printing (PLA) by superficially functionalizing the scaffold with oxygen plasma for required fixation and growth of osteocyte cells. **Materials and Methods:** To achieve the scaffold we used FDM 3D printer (Fused Deposition Modeling), called (Boa Impressão 3D), model Stella, Curitiba-PR, Brazil. The scaffolds were modeled (10 mm in diameter x 1 mm in height) in Autodesk Inventor CAD software and exported in the format STL. The Movitech filament with a diameter of 1.75 mm was used for the extrusion of PLA. To increase the roughness, we used the functionalization of the oxygen plasma on the surface of the scaffold. The system consists of a stainless steel reactor (~ 5.2 x 10-3m^3) containing two parallel circular electrodes with 11.9 cm in diameter, separated by 5cm. **Results:** We evaluated the contact angle (water) and it showed 38.95°; 16.5 °; 13.31°; 8.63 °; 29.88° for the times of 0,5 min, 1 min, 5 min, 10 min and 20 min respectively. Analyzing these results from the contact angle, were alized that the functionalization through oxygen plasma provided greater hydrophilicity to the PLA surface. We used AFM atomic force microscopy to investigate surface roughness and reached up to a 450% increase on the scaffold compared to an untreated scaffold. We submitted the functionalized scaffold to the proliferation and viability test with 1x10^5 Osteo-1 cells seeded in DMEM environment for 72 hours. We achieved 89 % of proliferation. We also noticed that increased roughness, caused by the oxygen plasma, increased cell adhesion and proliferation on the scaffold surface. **Conclusions:** It is understood that the scaffold obtained by extrusion of 3D printing with PLA and the functionalization with oxygen plasma promotes a better control of shape and size of the organ or tissue to be built, and imitates the extracellular matrix.

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The use of stem cells as a promising method for cardiac regeneration: current scenario and future prospects

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ABSTRACT

Introduction: Once cardiovascular diseases are the main cause of global mortality, there is high interest in the development of therapies for the reduction of the impact of these pathologies. The use of Stem Cells (SC) as a therapeutic method is a recent tactic for cardiac regeneration, justifying reviews about its current and future use. This technique is promising because it is able to provide cardiomyocytes after ischemic events, induce revascularization of the damaged area, and prevent deleterious pathological remodeling. **Objectives:** Analyze, through specialized literature review, the current scenario and future perspectives of the use of SCs for cardiac regeneration focusing obstacles and strategies of study. **Materials and Methods:** Articles from the last 6 years (2011 to 2017) were searched in the databases MEDLINE (accessed via PubMed), SciELO, LILACS, Scopus and Cochrane Library in English and Portuguese. The descriptors were: Stem, Cell, Cardiac, Heart, Regeneration, Repair and Therapy. Initial selection of articles was carried out based on the titles and abstracts and, after verification of the appropriate content, the complete text was searched. Thus, 55 articles that approached the theme were obtained. After reading, 23 texts that fully answered to the objectives of this research were selected. The most recent articles, with the highest impact factor and level of evidence were prioritized. Case reports and opinion articles were excluded. **Results:** The current scenario of SC implantation for cardiac regeneration is still little explored. The reviewed articles lists as difficulties in the study of the subject: heterogenic groups and methodologies, low long - term clinical follow - up of the volunteers and restricted number of works due to difficult access to suitable material and case – control groups. Not all types of SCs have already been studied. As obstacles to therapeutic applications, studies found that undifferentiated SCsmay induce teratomas and karyotype anomalies, genetic and immune rejection, immature phenotype (implanted cells tend to be more similar to their fetal counterparts), heterogeneity of SCs subtypes, and the difficulty of producing sufficient cells for effective repair. As control strategies, SC reprogramming techniques with non-viral vectors are being employed to avoid possible teratogenic events, addition of retinoic acid and manipulation of the Wnt differentiation pathway to obtain specific subtypes of cardiomyocytes and culture systems based on bioreactors to obtain adequate amount of cells. Combined gene and cell procedures are being used and developed in order to increase the survival of implanted SCs, such as cardiac patches in vitro, engineered heart tissue and injectable scaffolds. **Conclusions:** SC technology is an attractive approach to the generation of cardiac tissue, but studies face obstacles during research process that may affect its results. Long-term follow up studies and the development of combined gene and cell procedures can change this scenario.

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Influence of type 2 diabetes mellitus on cardiac regeneration after ischemic cardiomyopathy

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ABSTRACT

Introduction: Cardiovascular pathologies are the main cause of worldwide mortality. These diseases represent an estimated 80% of all deaths in diabetic patients. Once type 2 diabetes mellitus (T2DM) is an expanding global health problem, there is high interest in the understanding of the *physiopathological* influence of this condition on heart regeneration after ischemic events as well as development of appropriated therapies. **Objectives:** Analyze, through specialized literature review, the possible interventions against the negative effects of T2DM, focusing its *physiopathological* influence, on cardiac regeneration after ischemic cardiomyopathy. **Materials and Methods:** Articles from the last 7 years (2010 to 2017) were searched in the databases MEDLINE (accessed via PubMed), SciELO, LILACS, Scopus and Cochrane Library in English and Portuguese. The descriptors were: Type 2, Diabetes, Mellitus, Cardiac, Heart, Regeneration, Repair and Therapy. Initial selection of articles was carried out based on the titles and abstracts and, after verification of the appropriate content, the complete text was searched. Thus, 35 articles that approached the theme were obtained. After reading, 17 texts that fully answered to the objectives of this research were selected. Most recent articles, with the highest impact factor and level of evidence were prioritized. Case reports and opinion articles were excluded. **Results:** The elevated prevalence of cardiac disease with T2DM lead to studies of stem cell (SC) mediated heart repair in a limited number of patients and pre-clinical diabetic models. Some studies showed that mesenchymal stem cells (MSC) infused into diabetic rats with diabetic cardiomyopathy improved their heart function, lowered serum glucose and increased serum insulin levels compared with the control diabetic group (possibly through angiogenesis and attenuation of cardiac remodeling). It was noticed that MSC therapy promoted effective cardiac nerve sprouting, enhanced cardiomyocyte proliferation and increased endothelial cell incorporation into neovascularization, reducing heart complications in the presence of T2DM. However, studies also pointed that, in specific situations, T2DM inhibited the multipotency of MSCs and impaired their sufficiency to increase blood flow recovery. Hyperglycemia also showed deleterious effects on the role of endothelial progenitor cells in vascular and tissue repair, as well as affected the migration of cardiac SCs. On possible strategies to prevent or reverse the deleterious diabetic effect on SCs and cardiac regenerative therapies, articles suggest control of hyperglycemic state, reversal of oxidative stress, cardiac niche enhancement (to recover the cardiac homing capacity of SCs) and molecular modulation of specific targets (such as p38 MAPK and ERK1/2). **Conclusions:** The association of T2DM and cardiac diseases is relevant and a global health problem. The understanding of its *physiopathological* aspects can lead to better treatment options. Cardiac regeneration after ischemic cardiomyopathy with SCs is a promising therapy, still in development, that will require adaptations when applied to T2DM patients.

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Magnetic resonance imaging parametrization for threedimensional biomodels printing of patella joint cartilage

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ABSTRACT

Introduction: One of the most important causes of reduced body movement is osteoarthrosis (OA), the knee joint is the most involved and a fundamental component of this joint is patellar cartilage. Cartilaginous lesions lead to OA, fast or insidious, resulting from genetic, traumatic, vascular and metabolic alterations, leading to the irregularity of its surface and reduction of its thickness, aspects to be studied in detail. The spatial view of cartilage defects, as well as the monitoring of disease progression are of fundamental importance for the effectiveness of the treatment. It is not common to surgeons the three-dimensional (3D) idea of parts of the human body in the study and planning of conservative (clinical) and surgical treatment. **Objectives:** The objective of this research is to establish a higher quality parametrization for the acquisition of magnetic resonance imaging in order to obtain reliable three-dimensional biomodels of articular patellar cartilage through 3D printing technology. **Materials and Methods:** For this, a healthy individual, female, 25 years old and with no orthopedic antecedents or complaints compatible with patellar chondropathy was evaluated. The patient underwent magnetic resonance imaging of the knee in Magneton Essenza 1.5T equipment (SIEMENS®) coupled to a 14-channel radio-frequency coil. Axial images were established from the acquisition sequences T2-Gradiente, Proton Density (DP), T1- SpinEco, T1-Vibe and T2-GradienteEco (T2-GRE). The images were processed in the software InVesalius® and Magics® for the construction of three-dimensional biomodels in virtual environment. The recommended acquisition parameters for the generation of 3D biomodels of the patellar articular cartilage were established through a comparative analysis between the different acquisition sequences, considering the time spent in the image processing and the accuracy achieved in the virtual biomodels. **Results:** The results showed that all acquisition sequences allowed the generation of the 3D biomodels. In contrast, the processing parameters, the time spent performing the processing and the accuracy reached in the biomodels were significantly different among them. The best performance was achieved with the T1-Vibe acquisition sequence, which provided the shortest processing time and the highest accuracy of the three-dimensional biomodel. **Conclusions:** It is concluded that the parameters associated with this acquisition sequence are recommended for obtaining magnetic resonance imaging for the preparation of three dimensional biomodels for 3D printing. New research will be conducted to investigate the influence of other acquisition parameters, such as the field strength of the main magnet and the technical characteristics of the radiofrequency coil.

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Evaluation of the kinetic profile of the release of tetracycline in simulated gastric fluid and simulated intestinal fluid from biopolymer microparticles

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ABSTRACT

Introduction and Objectives: The aim of this paper was to prepare and characterize biopolymeric microparticles (MP) with bioadhesive properties to promote the sustained antibiotic release. The development of such devices aims to prevent early disruption of treatment protocol with antibiotics caused by lack of adherence from the patient, whose disruption is one of the causes of bacterial resistance increase. **Materials and Methods:** MP were prepared through mechanical shearing of chitosan (CH), sodium alginate (SA), and tetracycline hydrochloride (TC), whose amount followed an experimental design 2^3, whereby an influence of each component was observed in properties such diameter (D), encapsulation efficiency (%EE), and loading percentage (%LP). Diameters were measured on the Malvern Mastersize 2000 equipment. It was obtained particles with diameters between 4.5 and 8.5 µm were obtained. %EE was calculated through the relation between the difference of the total mass of TC (TM_{TC}) and the free mass of TC (FM_{TC}) and TM_{TC}. And %LP was calculated through the relation between the difference of the TM_{TC} and the FM_{TC} and the total mass of polymer. FM_{TC} was obtained through the liquid extracted by centrifugation at 10000 RPM for 10 minutes of 500 µL of MPs suspension placed in a ultrafiltration device Amicon® Ultra 0,5 MWCO 100K. TC was quantified by High performance liquid chromatography (HPCL) according to the Pharmacopoeia method of United Stated (USP 30 – NF 25, 2007). **Results:** %EE differed between 56% and 87% and %LP between 19% and 87%. Reagents and microparticles were characterized as to main functional groups identification by Fourier Transform infrared spectroscopy (FTIR); as to thermal stability by Differential Scanning Calorimetry (DSC). DSC tests indicated that preparations have less thermal stability with respect to pure reagents. FTIR spectra were recorded in the Fourier transform spectrometer, Agilent Cary, model 630 FTIR, with module ATR. FTIR spectra indicated the interaction between the CH, SA, and TC functional groups, which intensity differed according to the ratio of these compounds and affected both, loading percentage and encapsulation efficiency, as well as the release profile. Sustained release profile of TC in simulated body fluid with different PHs (simulated gastric fluid (SFG) and simulated intestinal fluid (SFI) were observed by 2h and 48h, respectively. These results suggest that there is a decrease of the burst effect in the TC release in both SFG and SFI, avoiding that the initial dose reaches a toxic level. Release profile in SFG is different than the observed in SFI, expected result, once the matrix constitutes of polyelectrolytes, which are sensible to the PH of solution. **Conclusions:** These results indicate that some microparticles are promising to a final formulation.

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Cytotoxic and mutagenic effects of new Cu(II) complex as potential antituberculosis agent

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ABSTRACT

Introduction: Since the discovery of the cytotoxic and antitumor activities of cisplatin, medicinal chemistry has seen impressive advances in the bioinorganic chemistry, with a growing interest in the study of the biological activities of metal complexes. In this context, copper (Cu) has a number of qualities that have made it attractive for such research, as it operates as a first-row transition metal, is the third most abundant trace metal in the human body (behind iron and zinc), is important for plants, animals and fundamental to the performance of several enzymes involved in energy metabolism, respiration, and deoxyribonucleic acid (DNA) synthesis. Previous studies showed that Cu(II) complexes, formed from the interaction of Cu(II) ions with biologically active ligands, have shown excellent antimicrobial activity against *M. tuberculosis*. **Objectives:** In view of this antimycobacterial activity and its potential as a lead compound for drug development, the aim of the present study was to investigate the mutagenic activity of Cu (II) complex with isoniazid $[Cu(NCO)_2(INH)_2]\_4H_2O$ (I3)], by the Ames test and the micronucleus assay, to assess the safe use of this complex in the treatment of tuberculosis, besides the cytotoxic activity in a normal cell line (GM-07492 - human lung fibroblasts) and a cell line with metabolism profile of carcinogens (HepG2) by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. **Materials and Methods:** The complex was synthetized in the Faculty of Pharmaceutical Sciences of Araraquara and provided by Dr. Patrícia Bento da Silva. The Ames test was performed using TA98, TA100, TA97a and TA102 strains of *Salmonella typhimurium*, as sensitive indicators of DNA damage, in the absence (-S9) and presence (+S9) of metabolic activation system in five concentrations, varying from 15.6 to 250 µg/plate. The micronucleus assay was performed in HepG2 cells in 3 different concentrations of I3, varying from 125 to 500 µg/mL. **Results:** The results obtained by Ames test showed that I3 induces only signs of mutagenicity in strains TA100 and TA97a tested in presence of metabolic activation. Similarly, it was observed a chromosomal damage in HepG2 cells with significant increases of micronuclei and nuclear budsand. With respect to cell viability, the complex induced a concentration-dependent decrease, but even so, the cytotoxicity (IC50) was higher than 500 µg/ml, indicating low toxicity. **Conclusions:** Further investigation is necessary to permit its more effective and safer use, beyond to clarify the mechanisms and the conditions that mediate the biological effects of Cu (II) complexes, before considering them as therapeutic agents.

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Nuclease activity of a copper complex with sulfameter

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Nuclease activity

ABSTRACT

Introduction: Copper complexes have a remarkable redox chemistry that has been explored for the development of artificial nucleases. The DNA damage is usually correlated to the anticancer and antibacterial activity of these copper compounds. **Objectives:** In this work, we report the nuclease activity of a copper(II) compound containing the sulfonamide sulfameter and 1,10-phenantroline as ligands. **Materials and Methods:** The copper compound was synthesized with 1:2:1 (copper(II) : sulfameter : phenantroline) ratio and characterized with chemical, spectroscopic and crystallographic techniques. For the evaluation of nuclease activity, two experiments were performed. Firstly, the plasmid pGEX4T-1 was incubated with the copper(II) complex and submitted to agarose gel electrophoresis. On the second experiment, ascorbic acid was added to the reaction mixture containing the plasmid and the compound. Copper(II) nitrate was also analyzed for comparison. **Results:** Results demonstrated that the complex alone alters the electrophoretic pattern of the plasmid, indicating some interaction, but no significant nuclease activity. Addition of ascorbic acid resulted in no visible band in the gel, indicating complete degradation of plasmid DNA at the complex concentration of 10 μmol·L^{-1}. Copper(II) nitrate, however, only altered the percentage of population of DNA in the supercoiled and partially supercoiled forms, but no complete degradation was observed up to the concentration of 20 μmol·L^{-1}. **Conclusions:** These results showed that the copper-sulfonamide is a promising compound for further biological studies.

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Palladium(II) and platinum(II) complexes with hydrazide derivative of nalidixic acid: synthesis and characterization

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ARTICLE INFO

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Platinum(II)
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ABSTRACT

Introduction: Platinum-based drugs are one of the most effective classes of antitumor agents. Nowadays, the Pt(II) complexes approved as anticancer agents are cisplatin, carboplatin and oxaliplatin, and it is estimated that they are used in 50% of all cancer treatments. A great effort has been made to develop new metal complexes with tumor-inhibiting properties better than cisplatin and its derivatives in efficacy, selectivity, reduced toxicity and improved pharmacology. Despite the endeavors to treat cancer more effectively, the pace of drug development is far from the current increasing rate of cancer incidence and mortality. To improve this scenario, one strategy of drug discovery is to combine the cytotoxic properties of a metal ion with the desired features of a specific ligand that have favorable safety profile and known pharmacokinetics. Nalidixic acid (1-ethyl-7-methy-1,8-naphthyridine-4-one-3-carboxylate, nx) is considered the precursor of the antibacterial quinolone series and is a interfacial inhibitor of DNA gyrase protein in bacteria. The inhibition of such enzyme causes a preferential, rapid and reversible inhibition of DNA synthesis. **Objectives:** In the present work, a modification of nx structure into a carbonyl hydrazide (hzd) was made and the obtained hydrazide was combined with Pt(II) and Pd(II) ions to further evaluate its antitumor activities. **Materials and Methods:** The hzd was synthesized from nalidixic acid following the procedure previously reported by our research group, and both complexes were synthesized by very similar routes, in which 0.50 mmol of hzd in methanol is reacted with 0.50 mmol of K_2PtCl_4 or K_2PdCl_4 in water, heated at 50°C for 2 hours under stirring and then stirred for additional 16 hours. **Results:** For both complexes, insoluble yellow solids were obtained, separated by filtration and washed with water and methanol. Calcd. for Pdhzd or $Pd(C_{12}H_{14}N_4O_2)2Cl_2$ (%): C, 43.03; H, 4.21; N, 16.73. Found (%): C, 44.22; H, 4.39; N, 16.84. Calcd. for Pthzd or $Pt(C_{12}H_{14}N_4O_2)2Cl_2$ (%): C, 38.00; H, 3.72; N, 14.77. Found (%): C, 37.53; H, 3.70; N, 14.26. Nitrogen solid state nuclear magnetic resonance spectroscopy indicated that coordination of the ligand to the metal centers occurs by the NH_2 group of hzd as the signal of the nitrogen atom of free ligand is shifted by -40.3 and -37.7 ppm in the Pdhzd and Pthzd complexes, respectively. **Conclusions:** This hypothesis is also supported by the infrared spectroscopic data of the complexes, where changes in the stretching modes of the NH2 group are observed. Biological studies are in progress.

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Synthesis and cytotoxic activity on Pd(II) complexes containing thiosemicarbazide

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ARTICLE INFO

Keywords:
Pd(II) complexes
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IR and NMR spectroscopy
Medicinal chemistry
Antitumor activity

ABSTRACT

Introduction: The interest on introduction of transition metal ions aiming at designing new chemotherapeutic agents has been prompted by the discovery of medicinal uses of cisplatin in treatment of several types of human neoplasms. Particularly, palladium(II) compounds have attracted considerable attention because of the analogy between the coordination chemistry of Pd(II) and Pt(II) complexes. In order to increase the kinetic stability of Pd(II) compounds, N,S-chelating ligand have been successfully employed to enhance the activity of these species in the cellular medium. Thiosemicarbazide is a N,S-chelating ligands capable to coordinate via sulfur and nitrogen atoms, affording a stable five-memberedring. For this reason, this ligand would be of interest to prepare new biologically active Pd(II) complexes. **Objectives:** Thus, we present here in the synthesis and cytotoxic evaluation against of the complexes of the type [PdX(tscz)PPh_3]X, where tscz = thiosemicarbazide, PPh_3 = triphenylphosphine and X = Cl^-(**1**) or I^-(**2**). **Materials and Methods:** Compound **1** was obtained from the reaction between [$PdCl_2(CH_3CN)_2$] and thiosemicarbazide (tscz), with further addition of triphenylphosphine. Complex **2** was synthesized by substitution of the chlorido group by iodide. The compounds were characterized by elemental analysis, IR spectroscopy, and ^1H and ^{13}C NMR spectroscopy, differential thermal analysis (DTA), and thermogravimetry (TG) and conductivity measurements. The cytotoxic activities of the complexes have been evaluated in vitro by MTT assay against two cell lines: human lung fibroblast (MRC-5) and human lung carcinoma (A549). For comparison purposes, the cytotoxicity of cisplatin, a standard metal-based antitumor drug, was also evaluated under the same conditions. **Results and Conclusions:** According to the cytotoxicity data, the free ligand tscz is considered inactive. The cytotoxicity of **1** and **2** against A549 cells was 10.46 and 11.27 μg/mL, respectively, being the value found for cisplatin 36 μg/mL. With regard to MCR-5 cells, both Pd(II) complexes displayed similar IC_{50} values (**1**: 3.06; **2**: 3.17 μg/mL), being more toxic than cisplatin (9.3 μg/mL).

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Flow cytometry studies over NCI/ADR-RES tumor cells of a silver(i) complex with 5-fluorouracil: preliminary results

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ARTICLE INFO

Keywords:
Flow Cytometry
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ABSTRACT

Introduction: In our previous work, we showed the antiproliferative activity of a silver(I) complex with 5-fluorouracil (Ag-5fu) against multi-resistant ovarian tumor cells (NCI/ADR-RES) when compared to free 5-fluorouracil (5fu), silver nitrate ($AgNO_3$) and cisplatin. The enhanced activity of Ag-5fu appeared to be a synergistic effect between 5fu and $AgNO_3$, when comparing their antiproliferative profiles. **Objectives:** Therefore, for a better understanding of the role of 5fu and silver(I) in the anticancer activity of Ag-5fu, we performed flow cytometry studies over NCI/ADR-RES tumor cells, comparing the effects of Ag-5fu, 5fu and $AgNO_3$ on cell cycle arrest and apoptosis induction. **Materials and Methods:** The multi-resistant human ovarian tumor cell line NCI/ADR-RES was obtained from the National Cancer Institute (Frederick-MA, USA). Stock cultures were grown in complete medium (RPMI 1640 supplemented with 5% FBS and 1% penicillin/streptomycin) at 37°C with 5% CO_2. Solutions of the compounds 5fu, Ag-5fu and $AgNO_3$ were prepared in complete medium and different concentrations were used for the assays. For cell cycle arrest: 0.75 μg mL-1 and 1.5 μg mL-1 for 5fu and $AgNO_3$, and 1.5 μg mL-1 and 3.0 μg mL-1 for Ag-5fu. For apoptosis induction (nexin): 1.5 μg mL-1 for 5fu and $AgNO_3$, and 3.0 μg mL-1 for Ag-5fu. The chosen concentrations were based on the metal:ligand proportion of the Ag-5fu complex (1:1 in mass). Cells were seeded in 6 and 12 well plates ($5x10^4$ cells/mL) for cell cycle and nexin assays, respectively, for 24h prior to treatment with the compounds. Flow cytometry experiments were performed in a Guava EasyCyte Mini Flow Cytometer (Millipore, MA, USA) using Guava Cell Cycle and Nexin reagents (Merck Millipore) according to manufacturer's instructions. For all assays cells without treatment were used as negative controls. For cell cycle arrest cells were treated for 36h, while for nexin assay cells were treated for 18h. **Results:** Cell cycle assay showed the arrest in G1 phase by 5fu and Ag-5fu, but no for $AgNO_3$, which did not arrest cell cycle in 36h. Nexin assay showed the induction of apoptosis for Ag-5fu and $AgNO_3$, but not for 5fu, which did not cause cell death for 18h of treatment. The Ag-5fu complex showed 11% cells marked only with annexin-V and 49% cells double marked with annexin-V and 7-AAD, in contrast to 8% and 28% for $AgNO_3$, respectively. **Conclusions:** These results show that in the Ag-5fu complex cell cycle arrest is caused by 5fu, while cell death seems to be triggered by apoptosis and caused by silver(I).

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Complexes of V, Pt and Pd with amino acids and a-hydroxycarboxylic acids

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ARTICLE INFO

Keywords:
Flow Cytometry
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Anticancer Activity

ABSTRACT

Introduction: Complexes of Pt(II), Pd(II) and V(IV,V) show cytotoxic activity on tumor cells, but their low selectivity causes acute side effects. There are many works published in the literature that report that the structural modification of the complexes by using modified ligands is an effective method to enhance their activity as chemotherapeutic agents and decrease the side effects. **Objectives:** The main goals of the present work are the synthesis of new complexes of V, Pt and Pd with amino acids, amino acid derivatives and α-hydroxycarboxylic acids and to test the *in-vitro* cytotoxic activity. **Materials and Methods:** The amino acids and the α-hydroxycarboxylic acids were used in their anion form. In general, the complexes were prepared in aqueous solution under reflux by using the molar proportion 1M:1L and 1M:2L. Complexes of V with glutamic acid, lysine, 2,2-bypiridin, cysteine, gabapentin, phthalic, mesaconic and orotic acids were obtained and are being characterized. Complexes of Pt with 5-FU (5-fluouracil) and phthalic and mesaconic acids were obtained using the same procedure and were partially characterized. These complexes were tested with mouth and neck cancer cell lines. Complexes of Pt(II) and Pd(II) with gabapentin and orotic acid were obtained and are being tested for mutagenic and cytotoxic activity on different cell lines. **Results:** Preliminary results show that the cytotoxic activity of the Pt-5-FU complex is lower than cisplatin and higher than free 5-FU. Pt complexes with phthalic and mesaconic acids did not show any cytotoxic activity. This fact can be explained by the oxidation of Pt(II) to Pt(IV) during the synthesis and a new synthetic method has been tested. **Conclusions:** Additional studies will be necessary to elucidate the structure of the complexes and the cytotoxic activity for different types of cancer cells.

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Study of the mutagenic potential of a new platinum complex by ames test

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Metal Complex
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ABSTRACT

Introduction: Over the years there has been a continuous interest in the chemistry of metal complexes, because of their key role in clinical therapy in biological applications of metal coordination compounds of biologically active ligands. Transition metals are particularly suitable for this purpose because they can adopt a wide variety of coordination numbers, geometries and oxidation states in comparison with other main group elements. However, one of the most important negative biological effects is the damage to DNA, since increases in DNA damage are associated with higher incidence of cancer and other different undesirable health consequences, including infertility and genetic disorders. **Objectives:** Whereas, carcinogenicity and mutagenicity are among the toxicological effects that cause the highest concern for human health, the aim of this study was to investigate the mutagenic activity of the platinum complex with mesaconic acid (Pt-Mesac) by Ames test, a widely used assay that detects mutations at the gene level through strains genetically modified of the *Samonella typhimurium* bacteria. **Materials and Methods:** Pt complex was produced and provided by the doctoral student Filipe Payolla, under the responsibility of Prof. Dr. Antônio Carlos Massabni. The Ames test was performed using TA98, TA100, TA97a and TA102 strains of *S. typhimurium*, as sensitive indicators of DNA damage, in the absence (-S9) and presence (+S9) of metabolic activation system in five concentrations, varying from 12.5 to 100 μg/plate. **Results:** The results obtained showed that Pt-Mesac was not mutagenic under the conditions used, because did not induce any increase in the number of revertant colonies relative to the negative control. **Conclusions:** The absence of mutagenic effect by Pt complex against *S. typhimurium* bacterial strains in the Ames test is highly relevant. However, further pharmacological and toxicological investigations are necessary to determine the mechanism(s) of action to guarantee their safer and more effective application to human health.

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Synthesis, characterizationand antibacterial activities of a new Au(III) complex with hydrochlorothiazide

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Au(III)
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Antibacterial activities

ABSTRACT

Introduction: The discovery of antibiotics can be considered one of the most significant achievements of modern science for the control of infectious diseases. However, the microbial resistance to antibiotics in use nowadays turns important the search for new compounds with better therapeutic efficiency and lower potential of development of bacterial resistance. One of the strategies to defeat the multiresistance is to combine metal ions, such as silver and gold, with ligands that already possess biological activities and further evaluate their efficacies as novel antibacterial agents. Gold compounds, in special, have been considered as antibacterial agents since the discovery of the antimicrobial activities of potassium dicyanoaurate(I) by Robert Koch in the end of the 19th century. Nowadays, gold compounds are mainly used as antiarthritic compounds, with emphasis to auranofin. Hydrochlorothiazide (HCZ), 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7sulfonamide 1,1-dioxide, a thiazide diuretic, is often used in combination with other agents in the treatment of hypertension and patients with ischemic diseases. In the view point of coordination chemistry, HCZ can be considered versatile ligand, being able to coordinate to metal ions such as Au(I,III). **Objectives:** Based on these considerations, a new Au(III) complex with HCZ, hereby identified as Au-HCZ, was prepared and evaluated about its antibacterial activities. **Materials and Methods:** The Au-HCZ complex was synthesized by the reaction of HCZ with $Li[AuCl]_4$ in an aqueous/alcoholic solution at pH 10. Elemental analysis indicated a 1:1 metal:ligand composition. Anal. calc. for $AuC_7H_7Cl_3N_3O_4S_2$ (%) C, 14.9; H, 1.25; N, 7.44. Found (%) C, 14.4; H, 1.40; N, 6.80. The FTIR spectrum of the complex was evaluated in comparison to that of free HCZ. Changes in the absorption bands of the vibrational modes of the N-H groups suggest nitrogen coordination to Au(III). Antimicrobial activity of Au-HCZ was preliminarily evaluated by disc diffusion and further confirmed by minimum inhibitory concentration (MIC) assays against bacterial strains *Staphylococcus aureus* ATCC25923, *Escherichia coli* ATCC25922 and *Pseudomonas aeruginosa* ATCC27853. **Results:** The MIC assay demonstrated the inhibitory activity of the complex against the considered strains with values of 2.13 mmol L^{-1} for *S. aureus*, 1.07 mmol L^{-1} for *E. coli* and 1.07 mmol L^{-1} for *P. aeruginosa*. **Conclusions:** Further studies are envisaged to confirm the potential of application of the Au-HCZ complex for treatment of bacterial infections.

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Physical-chemical characterization and cellular viability study of *baccharis dracunculifolia* plant extracts

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ARTICLE INFO

Keywords:
Vegetable extract
Baccharis dracunculifolia physicochemical characterization

ABSTRACT

Introduction and Objectives: *Baccharis dracunculifolia* (BD), also known as field rosemary, occurs naturally in the South, Southeast and Center-West of Brazil, mainly in cerrado regions. Young BD leaves are formed by tectonic and glandular trichomes, and contain volatile and aromatic oils. Those oils give BD the typical aroma of the green propolis, produced by the insect *Apis mellifera*. Diverse therapeutic activities are available in the literature, and it is possible to highlight the anti-inflammatory, antioxidant, antimicrobial, immunomodulatory, cytotoxic, hepatoprotective and antimutagenic activities. Development of new DB-based systems requires knowledge about its chemical profile and cell viability. Physical-chemical characterization of BD vegetal extracts (VE) and cell viability tests, through MTT assay, are the main focus of this work. **Materials and Methods:** VE is provided by Ciclo Farma Indústria Química Eireli chemical industry, located in Serrana – SP – BR. Determination of flavonoids were performed by UV/Vis spectroscopy, and the same extracts have also been subjected to fibroblast cell viability assays. **Results and Conclusions:** Up to the present moment, the presence of phenolic compounds and flavonoids, such as, caffeic acid, coumaric acid, Artepelin C, quercetin, rutin can be confirmed in the BD extracts. Cytotoxicity of VE is dose-dependent, and can be tuned by BD concentration.

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Search for high-added value compounds from soya crops agricultural waste

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ARTICLE INFO

Keywords:
Isoflavones
Soy
Agricultural waste

ABSTRACT

Introduction: It is estimated that a quarter of the approximately 140 billion tons of agricultural biomass produced per year worldwide is produced in Brazil, and that more than 30% of the total waste produced in this country are agricultural wastes. According to the United Nations, there is the need to intensify research on technologies for converting agricultural waste into useful resources to society. Furthermore, the search for compounds of interest in waste by means of advanced value-added strategies based on green technologies, before adding them to low value-added products, has been seen as a business opportunity. Soya crops corresponds to almost 60% of total cultivated are in Brazil having a strong impact in Brazilian GDP, but also in the generation of agricultural waste in Brazil. Soybeans are known to be one of the main sources of isoflavones, a class of flavonoids with innumerable properties for human health. Isoflavones rich extracts of soy beans are largely commercialized for the treatment of women who are going through climacteric. **Objectives:** This work aimed to investigate the potential of soya agricultural wastes (stems, leaves and twigs of soybeans) as raw materials for the preparation of phenolic rich extracts based on green solvents. **Materials and Methods:** Samples were extracted by dynamic maceration and analysed by HPLC-DAD/UV. **Results:** Overall, the greener ethanol and acetone provided better extractions than those observed for the reference solvent acetonitrile, an undesired chemical from the sustainability point of view. Isoflavones were found in stems and leaves together with other flavonoids, whereas the twigs showed to be a rich source of flavones. **Conclusions**: These residues showed potential to be raw materials for the production of flavonoid rich extracts rather than simply waste. The green solvents ethanol and acetone were able to replace acetonitrile for such extractions.

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Curcumin-cinnamaldehyde hybrids against *Xanthomonas citri* subsp. *citri*

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Keywords:
Xanthomonas citri subsp. *citri*
Curcumin
Cinnamaldehyde

ABSTRACT

Introduction: Citrus canker is one of the most aggressive citrus diseases, affecting the cultivation of citrus plants in some tropical areas. This disease is caused by *Xanthomonas citri* subsp. *citri* (Xac) and occurs in major orange juice producing countries, including Brazil and the USA. Chemical control of this disease has become ineffective, due to irrational use of cupric compounds. Recently, it was identified copper-resistant genes in Xac, which difficulted its eradication. Nevertheless, efforts are needed to identify and develop innovative anti-Xac compounds. Molecular hybridization is a widely used medicinal chemistry tool for design of bioactive compounds, we purposed hybridization using curcumin and cinnamaldehyde. Curcumin and Cinnamaldehyde are natural products used in cooking and medicine that exhibit broad spectrum antibacterial action against Gram-positive and Gram-negative species. **Objectives:** The objective of this work was to evaluate anti-Xac activity of curcumin-cinnamaldehyde hybrids (CCH). **Materials and Methods:** Firstly, a series of CCH (**1**-**12**) was synthesized and their structures were confirmed by 1 H and 13 C NMR. The minimum inhibitory concentration (MIC) of compounds against Xac was performed by the Resazurina Microtiter Assay. **Results:** Among evaluated compounds, **12** showed greater potency, with MIC value of 42.94 μg mL-1. Its minimum bacterial concentration (MBC) was determined at 100 μg mL-1 and compound **12** inhibit Xac growth. Thus, **12** was selected for Xac cell treatment evaluation by measuring the cell multiplication capacity in artificially inoculated plant tissues through the pathogenicity assay. In planta assay was performed on sweet orange "Pera Rio" (*Citrus sinensis*). Seedlings were contaminated by Xac and subsequently treated by **12** at concentrations of 2xMIC and MIC. Canker incidence was evaluated weekly. Treatments performed with **12** inhibited the Xac growth in both concentrations. **Conclusions**: In conclusion, curcumin-cinnamaldehyde hybrids are promising compound against Xac. Furthermore, design by molecular hybridization was effective because curcumin and cinnamaldehyde separated were not able to demonstrate significant bacterial death.

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Bioinspired surgical clip and coated with natural drugs from the Amazon

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ARTICLE INFO

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Surgical clip
Coating
Drugs from Amazon

ABSTRACT

Introduction: The suture is the closing of edges of a wound to approach tissues and to seal blood vessels. The use of ant mandible to suture wounds has been reported approximately 1,000 years BC, quoted in the Indian medical text *Charaka Samhita*. The specie used in this process was the *Atta laevigata* ant, because it has adequate size for manipulation, design and its biomechanics are perfect for opening and closing the mandible and to approach the edges of the wound. In addition, the species releases through the mandible a substance that works as an antibacterial agent for the injury, making this natural system self-sufficient in the suture. Based on this knowledge, it was developed the surgical clip bioinspired (MU9102934-1). The new mechanic system facilitates the handling both in its placement of the clip and also in its removal from the skin, which is less traumatic and efficient for the patient than the traditional clamping devices. The surgical clip will be coated with *Carapa guianensis* oil, popularly known as Andiroba and *Pterodon emarginatus* oil, popularly known as Sucupira. These oils are extracted from medicinal plants of the Amazon and they are traditionally used by Riverine peoples. The natural oils present efficient analgesic, anti-bacterial, anti-inflammatory, anti-fungal and anti-allergic properties and they were also found to be effective in the healing process. **Objectives:** The objective of this work is to coat the surgical clip with natural antibacterial oils improve its performance in the healing process. **Materials and Methods:** In this work, the coatings using the solution composed by natural oils and acetone were dip coated on the surface of the material AISI 420 after different intervals of time of immersion and drying. In addition, the natural oils characterization was carried out using the Fourier Transform Infrared Spectroscopy- FTIR. The adhesion of the oils to the clip surface was evaluated by morphological analysis: Electron Microscope Scanning - SEM and Microscope of Atomic Strength - AFM, including the verification of the *in vitro* cytotoxicity potential of the surgical clip coated with drugs. **Results:** The adherence results of the solutions on the AISI 420 samples surface were similar after 30s, 1min and 1.5min of immersion, as well as after 2min, 4min and 6min of drying, respectively. In addition, the coated samples proved to be effective on bioassays conducted with bacteria and fungi. **Conclusions**: The results support the traditional use of natural oils as antibacterial agents. They can be considered promising coatings on the bioinspired surgical clip.

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Study on the mutagenic potential of kaurenoic acid, a bioactive diterpenoid present in Copaiba oil, by Ames test

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ABSTRACT

Introduction: Plants that belong to *Copaifera* spp. are rich in kaurenoic acid, a diterpene that showed a wide variety of interesting biological activities, including antiparasitic and antimicrobial effects, anti-inflammatory action, and cytotoxicity against human cancer cells and hemolytic effects against mouse erythrocytes. However, previous studies showed that exposure of V79 cells to higher concentrations of kaurenoic acid caused significant increases in cell damage index and frequency. **Objectives:** To complement the results of the literature, their mutagenic activity was assessed by Ames test in this study. This assay detects mutations at the gene level through strains genetically modified of the *Samonella typhimurium* bacteria. **Materials and Methods:** In this study, it was performed using TA98, TA100, TA97 and TA102 strains of *S. typhimurium* in the absence (-S9) and presence (+S9) of metabolic activation system, in five concentrations, varying from 25 to 200 µg/ plate, established in previous cytotoxicity studies. **Results:** The results obtained showed that kaurenoic acid was not mutagenic under the conditions used, because did not induce any increase in the number of revertant colonies relative to the negative control. **Conclusions**: The absence of mutagenic effect against *S. typhimurium* bacterial strains in the Ames test is highly relevant. However, in light of the above and of the findings of the literature, it is necessary to clarify the conditions and the mechanisms that mediate the biological effects of kaurenoic acid before treating it as therapeutical agent, because the balance between the therapeutic vs. the toxicological effects is an important parameter in assessing its applicability in relation to phytotherapeutic potential.

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Evaluation of the Cytotoxic activity of standardized extracts of *myrcia bella* cambess. (Myrtaceae)

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ABSTRACT

Introduction: Plant-based systems continue to play an essential role in healthcare, and their use by different cultures has been extensively documented. Moreover, medicinal plants have historically proven their value as a source of molecules with therapeutic potential, and nowadays still represent an important pool for the identification of novel drug leads. Myrcia bella, a common and important species in many savanna fragments, distributed in the state of Sao Paulo, has potential use in the traditional medicine for treatment of diabetes mellitus. However, little is known about their undesirable properties such as mutagenicity, carcinogenicity and toxicity. **Objectives:** Thus, the aim of this study was to investigate the cytotoxicity of standardized extracts (70% ethanol) of leaves of M. bella. **Materials and Methods:** Cytotoxicity was assessed by changes related to metabolic functions of mitochondria detected by a colorimetric method known as MTT (tetrazolium 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) in a normal cell line (GM-07492 - human lung fibroblasts) and a cell line with metabolism profile of carcinogens (HepG2 - human hepatocellular carcinoma). **Results:** According to the results, M. bella induced a statistically significant reduction on cell viability of the HepG2, in all concentration tested compared to the negative control. In the treatments with the GM-07492 cultures, M. bella revealed lack of cytotoxicity; cell viability of the extract was greater than 80% **Conclusions**: The results obtained in this study are extremely relevant because it provides reliable data to support future clinical researches. However, further toxicological tests are needed to ensure its safe use.

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Toxicity evaluation of cinnamylideneacetophenones against human cervical cancer cells positive for HPV16 and HPV18

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ABSTRACT

Introduction: Human Papilloma Virus (HPV) is the main causative agent of cervical cancer, including HPV16 and HPV18 types, which have been found in 99% of cases. In worldwide, cervical cancer is the most common cause of cancer related deaths among women. In Brazil, cervical cancer is the third most frequent tumor, with 5.430 cases of deaths reported by INCA. It was estimated 16.340 new cases reported in 2016. Thus, there is a need for innovative compounds against cervical cancer. In this context, screening of natural compounds constitutes an valuable alternative for the discovery of antineoplastic agents. Cinnamaldehyde is the main chemical constituent of essential oil from *Cinnamomum cassia*. This compound has demonstrated to be an cytotoxic agent against several human cancer cells. **Objectives:** Thus, the objective of this work was to evaluate toxicity of named as cinnamylideneacetophenones (cinnamaldehyde derivatives) against human cervical carcinoma cells positive for HPV16 (CaSki ATCC CRM-CRL-1550) and HPV18 (HeLa ATCC CCL-2). **Materials and Methods:** Cells were treated with substances **1** – **4** and cinnamaldehyde, which was used as a positive control, in concentrations ranging from 0.75 to 800 μmol L^{-1} to derive IC_{50} (concentration capable of inhibiting 50% of the cells). Cellular viability was evaluated after 48 h by MTT assay. This methodology evaluates cell metabolic activity, measuring on spectrophotometer the reduction tetrazolium bromide in formazan by activity of mitochondrial dehydrogenases. The experiments were performed in triplicate and in three independent assays. Statistical analyses were performed by one-way ANOVA with Tukey's post hoc test using Graph-Pad Prism 7.0 software. **Results:** Out of 4 compounds, **2** showed the highest toxicity against CaSki and **4**, demonstrated toxicity against HeLa, exhibiting IC_{50} values of 37.78±8.20 and 59.13 ± 2.41 μmol L^{-1} respectively ($p<0.01$ vs. control). Cinnamaldehyde was not able to inhibit cell growth (IC_{50} >100 μmol L^{-1}). It is suggested cinnamylideneacetophenones **2** and **4** were more potent than cinnamaldehyde. The presence of hydroxyl group at 3' position on ring A, increased cytotoxicity. **Conclusions**: In conclusion, **2** and **4** demonstrated superior cytotoxicity, when compared to cinnamaldehyde. These compounds are hits for development of new agents useful for cervical carcinoma treatment.

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Synthesis, antibacterial and antitubercular activities of cinnamaldehyde derivatives

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ABSTRACT

Introduction: Cinnamaldehyde (CMD) is the majority component in cinnamon bark oil, and it is responsible for its spicy and sweet. The spectrum of antibacterial activity of CMD has been extensively reported and includes effects against Gram-positive, Gram-negative and mycobacteria species. The mode of action of CMD involves bacterial multi-targets, including membrane disruption, cell division inhibition, and reactive-oxygen species induction. CMD possess aliphatic aldoxyl group, which is an undesirable functionality due to its high reactivity. **Objectives:** Herein, we designed and synthesized a series of derivatives with the replacement of aldoxyl group by acetophenone moiety. **Materials and Methods:** Their antibacterial and antitubercular activities were evaluated against Gram-positive and Gram-negative species, as well as *Mycobacaterium tuberculosis*. In addition, hydrophilicity of all compounds was measured by HPLC-PAD experiments, which enabled calculation of partition coefficients (log *P*o/w). Synthesis of derivatives was achieved by aldol condensation between CMD and corresponding acetophenone under basic catalysis, at room temperature. For antibacterial and antitubercular evaluations were used *Staphylococcus aureus* ATCC 14458 *(Sa)*, *Streptococcus mutans* ATCC 25175 *(Sm)*, *Streptococcus sanguinis* ATCC 10557 *(Ss), Pseudomonas aeruginosa* ATCC 15442 *(Pa), Escherichia coli* ATCC 10536 *(Ec), and M. tuberculosis* ATCC 27294 *(Mt)*. MIC and MBC were determined by broth microdilution method, in 96-well microtiter plates. We calculated the log *P*o/w by using HPLC-PAD method suggested by OECD protocols. **Results:** Phenolic derivatives **2** and **3** exhibited MIC and MBC values of 19.5 to 78.1 μg/mL against *Sa, Sm, and Ss*. Also, amino- (**4**) and vanillyl- (**7**) derivatives exhibited activity against *Sm* and *Sa* (MIC = MBC = 78.1 μg/mL). Derivatives bearing hydrophobic and electron-with drawing substituents were inactive against *Sa*, *Sm* and *Ss*. These results indicate electron-donating and hydrophilic groups enhanced antibacterial activity. Bioactive derivatives against Gram-positive species were not able to inhibit Gram-negative species growth. Compounds **1**, **6**, **9**, and **17** presented potent effects against *Mt* (13.2 μg/mL ≤ MIC ≤ 23.4 μg/mL). The electronic nature of substituent was not relevant for antitubercular activity. Anti-*Staphylococcus* and anti-*Streptococcus* compounds exhibited log *P*o/w values ranging from 2.5 to 3.3. Among these, **2** and **3** were the most potent, with log *P*o/w values of 2.7 and 2.6, respectively. The four most active anti-*Mycobacterium* compounds presented log *P*o/w values ranging from 3.2 to 3.5. Highly hydrophobic compounds displayed log *P*o/w > 3.5 and were not able to act against *Sa*, *Sm, Ss,* and *Mt*. Preliminary structure-activity relationship (SAR) investigations suggested hydrophilicity is central parameter for antibacterial and antitubercular activities of CMD derivatives. **Conclusions**: Furthermore, our results corroborated the potential of CMD as privileged starting material and template for synthetic collection of hits.

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Antimycobacterial activity of dehydrozingerone derivatives

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ABSTRACT

Introduction: Tuberculosis, an infectious disease of worldwide distribution, is considered a serious public health problem. The causative agent of tuberculosis is *Mycobacterium tuberculosis*, an aerobic bacterium, which has not capsule and spores. Emergence of resistant strains of *M. tuberculosis*, HIV co-infection and existence of latent intramacrophagic bacilli led to the search for innovative drugs, allowing greater adherence of the patient to treatment. Dehydrozingerone (DZG) is a phenolic compound from ginger rhizomes (*Zingiber officinale*). DZG has demonstrated several biological activities, such as: cardiovascular protection, anti-inflammatory, antitumoral, antimutagenic, antioxidant, antidepressive, anti-Alzheimer, antimalarial, antifungal, antibacterial and hypoglycemic. **Objectives:** This study aimed to synthesize and evaluate tuberculostatic activity of 10 DZG derivatives against *M. tuberculosis*. **Materials and Methods:** DZG derivatives were synthesized by aldol condensation reactions between DZG and benzaldehyde derivatives substituted by electron acceptor and donor groups, as well as hydrophilic and hydrophobic groups. For synthesis of DZG, it was used aldol condensation reaction between vanillin and acetone. DZG derivatives were evaluated *in vitro* against*M. tuberculosis* H37Rv strain (ATCC 27294) by broth dilution method coupled with the *Resazurin Microtiter Assay* (REMA). Compounds were tested in concentrations ranging from 25.0 to 0.09 μg mL^{-1} for determination of minimum inhibitory concentration capable of inhibiting 90% of *M. tuberculosis* growth (MIC_{90}). Rifampicin was used as reference tuberculostatic. **Results:** Derivatives **2**, **3**, **5**, **7**, **9** and **10** demonstrated antimycobacterial activity with MIC_{90} values ranging from 8.0 to 2.4 μg mL^{-1}. In general, it was observed that presence of *para*-substitutions on ring B by hydrophobic groups enhanced antimycobacterial activity, and eletronic nature of substituent was not relevant for tuberculostatic activity. In addition, it was evident that the cyclization, which promotes relative conformational restriction, triggered a decrease toward antimycobacterial activity. Therefore, structure-activity relationship data were observed, highlighting the influence of different hydrophobic groups on tuberculostatic activity. **Conclusions**: Furthermore, DZG derivatives corroborate the importance of natural products for the design of innovative tuberculostatic agents.

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Synthesis and anti-*staphylococcus aureus* activity of aminochalcones

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ABSTRACT

Introduction: Bacterial resistance is a natural phenomenon, which has been enhanced after use of antibiotics, generating superbugs, which are resistant to several drugs. The indiscriminate use of antibiotics, slow rate diagnoses and poor hospital hygiene are factors of bacterial resistance. Thus, the discovery of innovative antibacterial agents is necessary. Chalcones are privileged scaffolds in Medicinal Chemistry, which have exhibited broad spectrum of pharmacological activities, such as: antibacterial, antifungal, antimalarial, antiviral, antioxidant and anti-inflammatory. **Objectives:** The objective of this work was to synthesis and evaluation of 2'-, 3'- and 4'-aminochalcones against *Staphylococcus aureus.* **Materials and Methods:** A series of aminochalcones was synthesized by aldol condensation Claisen-Schmidt reactions between aminoacetophenone derivatives and benzaldehyde derivatives. Their antibacterial activity was tested against methicillin-sensitive *S. aureus* ATCC 25923 (MSSA) and methicillin-resistant *S. aureus* ATCC 33591 (MRSA). Bacterial susceptibility activity was expressed as values of Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC). Chalcones were tested in concentrations ranging from 0.48 to 62.5 μg mL^{-1}. Vancomycin was used as reference antibiotic. **Results:** Allaminochalcones substituted with amino group at 3' position of ring presented antibacterial activity. Among these, aminochalcone **3e** (3,4-Cl_2) exhibited the highest antibacterial potency against MSSA, displaying MIC value of 1.95 μg mL^{-1}. 2'-aminochalcone **2b** (4-Cl) demonstrated the highest anti-MRSA potency, demonstrating MIC value of 7.8 μg mL^{-1}. 4'-aminochalcones were not able to inhibit MSSA and MRSA growth. Aminochalcone **3e** was twice less potent than vancomycin, displaying MIC value of 1.95 μg mL^{-1} against MSSA. Furthermore, **3e** was eight times less active against MRSA (MIC = 7.8μg mL^{-1}). **Conclusions**: These results suggested 2 'and 3'-aminochalcones are promising *hit* antibiotics with biological potential similar to vancomycin.

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Synthesis and trichomonicidal activity of hydroxychalcones

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ABSTRACT

Introduction: Trichomoniasis, caused by *Trichomonas vaginalis*, is the most common non-viral sexually transmitted disease (STD) around the world. For the trichomonias is treatment, nitro-compounds, metronidazole and secnidazole are the most prescribed, although there are several resistant strains and severe adverse effects. Thus, the search for new trichomonicidal agents is urgent. **Objectives:** In the present work, hydroxychalcones were designed, evaluating importance of hydroxyl position on rings A and B, as well as ring B substituted by groups recommended by the Manual Method of Topliss. **Materials and Methods:** Chalcones were synthesized via aldol condensation reaction of Claisen-Schmidt. The structures of substances were confirmed by Nuclear Magnetic Resonance. The trichomicidal activity of the hydroxychalcones was evaluated against strains of *T. vaginalis* (ATCC 30236) with the concentration determination capable of inhibiting 50% growth (IC_{50}). These substances were submitted to toxicity tests against human vaginal epithelial cells (HMVII, ECACC 92042701) and the selectivity index values (SI) were established by the ratio of the lethal concentration (CL_{50}) and IC_{50}values (SI = CL_{50}/ IC_{50}). **Results:** Chalcones with hydroxyl on ring A exhibited activity against *T. vaginalis* higher than those with hydroxyl on ring B, being the first used for bioactivity optimization steps. Among these, the 4'-hydroxychalcone and 3'-hydroxychalcone showed higher antiprotozoal activity, displaying IC_{50} values of 27.5 and 49.4 μM, respectively. On the other hand, 2'-hydroxychalcone exhibited IC_{50} of 76.4 μM. However, hydroxychalcones did not show selectivity and were toxic to host cells, with SI of values ranging 0.5 to 1.1. **Conclusions**: The hydroxyl group at 3' and 4' position were crucial for trichomicidal activity. With draw and donating groups donors maintained and / or decreased potency for the 3' - hydroxychalcone and 4'-hydroxychalcone frameworks.

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In vitro bacterial reverse mutation assay: mutagenicity study of oleoresin of *copaifera langsdorffii*

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ABSTRACT

Introduction: In recent times, many studies have been directed towards the identification of natural products with therapeutic properties, given the increased use of plant products for cultural, medicinal and social purposes. These natural products can be used directly or may be extracted to identify new bioactive compounds. So, it is essential to evaluate their biological effects to minimise the potential risks to human health. In this context, studies concerning genotoxicity may indicate the safety and effectiveness of herbal health products. **Objectives:** Thus, the aim of this study was to investigate the mutagenic activity of oleoresin extracted from the trunk of *Copaifera langsdorffii* by the Ames test. **Materials and Methods:** In this study, the Ames test was performed using TA98, TA100, TA97 and TA102 strains of *Salmonella typhimurium* in the absence (-S9) and presence (+S9) of metabolic activation system, in five concentrations, varying from 0.5 to 4.0 mg/ plate. **Results:** The results obtained showed that *C. langsdorffii* oleoresin did not induce any increase in the number of revertant colonies relative to the negative control, indicating the absence of mutagenic activity. **Conclusions**: The absence of mutagenic effect by this oleoresin against *S. typhimurium* bacterial strains in the Ames test is highly relevant, and is a positive step towards ensuring its safe use in medicine. However, further pharmacological and toxicological investigations are necessary to determine the mechanism(s) of action to guarantee their safer and more effective application to human health.

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In vitro mutagenicity of *murraya paniculata* assayed by bacterial reverse mutation (Ames) test

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ABSTRACT

Introduction: The use of medicinal plants as alternative remedies has been increasing over time. The species of the genus *Murraya* has been traditionally used as an analgesic and local anesthetic for the treatment of eczema and rheumatism. *Murraya paniculata*, belonging to the Rutaceae family, has a great diversity of secondary metabolites. So, it has aroused interests in the research on its chemical, biological, chemosystematic and pharmacological aspects. However, despite being a natural extract and known by its popular use, little is known about its mutagenic potential. It is essential the evaluation the mutagenicity of extracts used by the population with therapeutic efficacy, since the cancer and other pathologies can come from mutations in the DNA. **Objectives:** Thus, the aim of the present study was to determine the mutagenic effects of the ethanolic extract of the leaves *M. paniculata* by the Ames test. **Materials and Methods:** The extract was produced and provided by the doctoral student Celia Magaly Casado Martin in the Laboratory of Pharmacognosy of the Faculty of Pharmaceutical Sciences of Araraquara (UNESP), under the responsibility of Prof. Dr. André Gonzaga. The Ames test uses bacteria as sensitive indicators of DNA damage, and a rat liver homogenate (S9 microsomal fraction) for metabolic conversion of carcinogens to their active mutagenic forms. In this study, the Ames test was performed using the preincubation methodology with TA98, TA100, TA97 and TA102 strains of *Salmonella typhimurium* in the absence (-S9) and presence (+S9) of metabolic activation system, in five concentrations, varying from 1.25 to 20 mg/ plate. **Results:** The results obtained showed that *M. paniculata* acted directly and its mutagenicity increased with metabolic activation. According to the strains involved, *M. paniculata* induces substitution of base pairs (TA100), and, at a much higher rate, frameshift mutations (TA98 and TA97a). **Conclusions**: Considering that the extract is a complex mixture of several unknown organic compounds, the mutagenicity observed may be explained in part by a synergy between compounds present in the extract. So, this plant should be used cautiously for medicinal purposes.

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