Revista ARACÊ
ISSN: 2358-2472

BACURI BUTTER TOPICAL EMULGEL (PLATONIA INSIGNIS MART.) AND PIROXICAM FOR THE TREATMENT OF ARTHRITIS: PRECLINICAL TRIALS

https://doi.org/10.56238/arev6n2-013

Submission date: 09/02/2024 **Publication date:** 10/02/2024

José Francisco Ribeiro[1], Maria do Livramento Fortes Figueiredo[2], André Luís Menezes Carvalho[3], Matheus Oliveira do Nascimento[4], Benedito Pereira de Sousa Neto[5].

ABSTRACT

Introduction: Several studies have focused on the search for pharmacological activities of bacuri butter (Platonia insignis Mart.), given the empirical use in inflammatory diseases. Thus, the aim is to examine the pharmacological activity of bacuri butter topical emulgel and Piroxicam in an experimental arthritis model. The emulgel is feasible regarding the organoleptic characteristics, physicochemistry and validation of methods of epidemiology.
Design: preclinical trial, consisting of the topical formulation of bacuri butter and piroxicam (F1) and topical formulation of bacuri butter (F2); held at the Federal University of Piauí (UFPI), Teresina, PI, Brazil; experimental research with data organization in the period from 2021 to 2022. The results obtained were submitted to analysis of variance (ANOVA), followed by Tukey's post-test, with the aid of the statistical software GraphPad Prism 6.0 (GraphPad Software, San Diego, CA, USA).
Results: The arthritis protocol was performed by induction of edema in Wistar's paw by carrageenan, monosodium urate salts, prostaglandin and zymosan. The emulgel exhibited selectivity, linearity, accuracy, precision, robustness, systemic and histological toxicity, and evidence of anti-edematogenic activities.
Implications: The emulgel has anti-arthritic and anti-inflammatory activities, low cost, easy access, pleasant color and odor, good adhesion, easy delivery process of the active ingredient to the site of pain.

Keywords: Platonia Insignis Mart, Anti-inflammatory Activity, Arthritis, Old, Gerontological Nursing.

[1] Federal University of Piauí
Graduate Program in Nursing
Health Sciences Center
ORCID: https://orcid.org/0000-0003-3133-010
[2] Federal University of Piauí
Graduate Program in Nursing
Health Sciences Center
ORCID: https://orcid.org/0000-0003-4938-2807
[3] Federal University of Piauí
Graduate Program in Pharmacy
Health Sciences Center
ORCID: https://orcid.org/0000-0002-4433-6203
[4] Federal University of Piauí
Graduate Program in Pharmacy
Health Sciences Center
ORCID: https://orcid.org/0000-0002-0586-5260
[5] Federal University of Piauí
Graduate Program in Pharmacy
Health Sciences Center
ORCID: https://orcid.org/0000-00015287-5034

Revista ARACÊ
ISSN: 2358-2472

INTRODUCTION

Arthrosis or osteoarthritis (OA) is the most frequent form of joint disease and mainly affects the joints of the hips, knees, hands and feet. In the United States of America (USA), it is estimated that 36.4% of people over the age of 60 exhibit OA on their knees.[1] In Brazil, the population of people aged 60 years and over in 2019 reached approximately 32.9 million, with an estimated decrease to 228.3 for the 2060s. This is alarming data, given the disabilities, loss of quality of life and expenses generated by this disease to the health system.[2]

In 2013, OA was evidenced as the primary diagnosis of 23.7 million outpatient visits in the USA, through this article it is verified that 32.5 million adults in the USA, 14% of the American population, revealed symptoms of knee osteoarthritis between 2008 and 2014. The incidence of knee osteoarthritis in the U.S. is predicted to be 240 people per 100,000 per year. The worldwide prevalence of radiographically proven symptomatic knee osteoarthritis (OA) is expected to be 3.8% overall, increasing with age to more than 10% in the population over 60 years of age.[3]

OA has several risk factors, most notably aging. This disease results mainly from the wear and tear of the cartilage that surrounds the bones. Thus, it can also cause problems in the ligaments, synovial membrane and synovial fluid. The disease intensifies over time and shows no cure, the treatment is linked to pain relief or prophylactic for strengthening the joints and inhibiting the advance of cartilage wear.[4.5]

Modern guidelines are attentive in the evaluation of glucosamine, chondroitin, turmeric, ginger extract, and vitamin D. Most of the evidence has confirmed some or no change in the outcomes of clients with knee osteoarthritis. Although the evidence does not robustly attest to an advantage for dietary supplements, the risks involved are totally minimal, with the main obstacle being cost, since dietary supplements usually constitute a direct cost for the user.[5.1]

The current guidelines have shown that oral nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are drugs of choice in the treatment of knee osteoarthritis. Evidence has confirmed the use of NSAIDs and acetaminophen, as these oral medications have proven solid improvement in arthritic symptoms. For non-selective and cyclooxygenase-2-selective oral NSAIDs, both are effective drugs.[6.1]

Although cyclooxygenase-2 selective oral NSAIDs have been produced for the purpose of mitigating gastrointestinal adverse events, there is no evidence to establish a

Revista ARACÊ
ISSN: 2358-2472

notable difference in the risk of a gastrointestinal side effect with non-selective NSAIDs. Although acetaminophen and NSAIDs are effective, it is important to understand the prescription, and adapt it to the patient's profile, especially if they are elderly, as well as to consider the use of some drugs for continuous use.[6]

Plants have aroused interest in research because they contain too many sources of medicinal operators for the care and cure of various diseases, reaching approximately 60% of the pharmaceutical market.[7] The demand for new drugs with plants has mobilized the discovery of numerous metabolites with notorious qualification for drug production through isolation, clarification of the structure, constitution and measurement of bioactivity based on phytochemical composition and applicability in conventional medicine.[8.7]

Platonia insignis is a species related to the Clusiaceae family easily found from the Amazon to Piauí, in which its fruit (bacuri) is quite edible in the natural way it is presented or processed.[9] Butter or oil isolated from bacuri seeds is often applied as a healing and anti-inflammatory.[10,11] There are publications in articles pertinent to this premise that express reports on seed extracts, fractions and isolated compounds tested in various biological activities and that these exhibited favorable responses such as reduction of oxidative stress,[11,12,13] elimination of parasites14,15 and enzymatic inhibition of α-glucosidase and acetylcholinesterase.[15,16] Immunomodulatory effects and low in vivo toxicity were also detected in extracts obtained from seeds.[17.18]

Platonia insignis *seeds* are rich in fatty acids, triacylglycerols, and metabolites with therapeutic ability, such as xanthones that exhibit antiepileptic and antiparasitic impacts.[13] and polyisoprenylated benzophenones, with vasorelaxant results in animal models18. A triacylglycerol detached from the hexane extract of its seeds, 1,3-diestearyl-2-oleylglycerol (TG1), in formulations, showed efficacy in wound healing in rats.[19] Therefore suggested as promising in relieving arthritic pain.

METHODOLOGY

TOPICAL FORMULATION OF BACURI BUTTER WITH THE ADDITION OF PIROXICAM (F1) AND TOPICAL FORMULATION OF BACURI BUTTER (F2)

The emulgel was obtained using Poloxamer 407 (lot 0087/54622) obtained from Embrafarma (Brazil); potassium sorbate and sorbic acid acquired from Nantong (Brazil); sodium hydroxide obtained from Vertec (Brazil); Piroxicam (Valdequímica, Brazil). Fresh bacuri butter (Lot: 004/0817) purchased from Amazon Oil (Brazil). For the preclinical trial,

Revista ARACÊ
ISSN: 2358-2472

carrageenan (Sigma, USA), 0.9% NaCl solution, distilled water, sodium bicarbonate (MERCK, Brazil), Histamine (Sigma, USA), Prostaglandin (MERCK, Brazil), bacuri butter gel and emulgel (LADERMO/UFPI), Zymosan (Sigma, USA), and commercialized Piroxicam emulgel (MERCK, Brazil) were obtained.

TECHNOLOGICAL ACQUISITION AND EVALUATION OF THE PRELIMINARY STABILITY OF TOPICAL FORMULATIONS OF BACURI BUTTER AND PIROXICAM (F1) AND TOPICAL FORMULATION OF BACURI BUTTER (F2).

Two formulations consisting of Poloxamer 407 powder plus potassium sorbate were obtained, dispersed in distilled water and refrigerated for 24 hours in a freezer at a temperature of 8 ±1ºC, thus forming the Polaxamer gel. After obtaining the gel, the bacuri butter (vegetable stratum) was taken to the heating plate in a water bath at 40ºC, followed by the dissolution of sorbic acid and 0.5% of piroxicam in it. Then, the gel was poured over liquefied butter at room temperature and mixed by means of a mechanical stirrer at 250 rpm for a period of 5 minutes, originating the bacuri butter emulgel with Piroxicam (F1). Subsequently, bacuri butter emulgel (F2) was constituted. (Chart 1).

Table 01. Description of the technological production of topical formulations of bacuri butter and piroxicam

Substances	Concentrations	Formulations obtained
Distilled water q.s.p	160 ml	Gel polaxamer
Polaxamer 407	25%	
Potassium sorbate	0,2%	
Gel polaxamer q.s.p	25%	Bacuri and piroxicam butter formulation (F1)
Piroxicam	0,5%	
Jaw butter	10%	
Sorbic acid	0,2%	
Gel polaxamer q.s.p	25%	Bacuri butter formulation (F2)
Jaw butter	10%	
Sorbic acid	0,2%	
Note: these concentrations were used to obtain 50 g of each formulation Source: Survey data		

For the evaluation of topical formulations *in vivo*, the following tests were performed: assays to determine the organoleptic characteristics (pH, sabability and oganoleptic characteristics) before and after the evaluation of thermodynamic stability. The quantification method of piroxicam was also validated in the F1 formulation, which was selective, linear, accurate, precise and robust. The *in vitro release test* in a closed diffusion system, as well as the other tests, complied with the recommendations of RDC, 166 and RDC 318, therefore tested and approved.[20, 21] months

Revista ARACÊ
ISSN: 2358-2472

EVALUATION OF THE ANTI-ARTHRITIC ACTIVITY OF BACURI AND PIROXICAM (F1) BUTTER FORMULATIONS AND BACURI BUTTER (F2) FORMULATIONS IN EXPERIMENTAL ARTHRITIS

A total of 180 adult males (128) and females (52) of the Wistar albino lineage, weighing 150-210g, from the Central Vivarium of the Federal University of Piauí, were kept in polypropylene boxes at room temperature of 22 ± 2ºC, with light/dark cycles of 12/12 hours, receiving standard diet and water *ad libitum*. For the application of the experimental protocols, they remained fasting from solids for 12 hours and divided into groups, at first a preliminary toxicity test was carried out with a group composed of n=8, this is justified by being a limiting test of fundamental importance for the continuity of the following methodologies. It is in this protocol that the possible toxic effect of the formulations under study is evaluated.

Continuing, the formulations obtained (F1 and F2) or vehicle, both topically, were administered, in addition to the standard drugs for the proposed protocols, topically, and after 30 or 60 minutes for absorption, in which the experimental protocols were applied. After the experimental procedures, the animals were euthanized with an overdose of sodium thiopental (100 mg/kg, i.p.), according to CFMV Resolution No. 1000, of May 11, 2012. The experimental protocols complied with the criteria of the Ethics Committee on Animal Experimentation of the Federal University of Piauí (CEEA/UFPI), according to approval letter No. 621/2019.

EVALUATION OF THE TOXICOLOGICAL ACTIVITY OF THE FORMULATIONS: F1 AND F2 IN AN ACUTE TOXICITY MODEL IN RATS

As there are no established toxicity studies in the literature for the formulations obtained, it was necessary to determine the acute toxicity of the test substances. For this, Wistar rats (*Rattus norvegicus*) were used, with a mass ranging from 170-270g.

The acute dermal toxicity study (t.v.) followed the recommendations described in OECD Guideline No. 40222. On the day before the test, the trichotomy of the dorsal area of all animals was carefully performed.[23, 24] For this activity, 12 rats were distributed into four groups: G (polaxamer gel), F1 (bacuri butter emulgel and 0.5% Piroxicam), F2 (bacuri butter emulgel) and M (bacuri butter). The gel formulations and bacuri butter were applied evenly on the clean skin of the animal at a dose of 2000 mg/kg body weight.[25.26]

Revista ARACÊ
ISSN: 2358-2472

The exposed surface area was approximately 10% of the total body area of the animal, calculated from the formula AST(m2) = 1.85. $(W/70)^{2/3}$, where AST is the body surface area and W is the weight in kilograms. The formula takes into account the human body surface considering the average value (1.85m2) for a 70 kg human.[27,28] After the pre-treatments, the animals were observed at intervals of 30, 60, 120, 180 and 240 minutes. Behavioral, functional and motor activity parameters were verified in all groups, then the animals were housed in individual cages for a period of 14 days.[22]

The variation in weight of the animals on the first, seventh and fourteenth days after treatment was also evaluated. Vocal thrill, irritability, response to touch, contortion, straightening reflex, muscle tone, ataxia, auricular reflex, corneal reflex, tremors, convulsions, hypnosis, anesthesia, tearing, eyelid ptosis, urination, bowel movements, piloerection, breathing, cyanosis, hyperemia, and death were also verified. Their intensity, duration and progression were recorded, tabulated on a scale of 0 to 4 (absent, rare, little, moderate, intense) for later analysis. [22]

During the evaluation period of the parameters that express some signs of acute toxicity, we also sought to determine the persistence or delay in the occurrence of toxic effects. Finally, all animals were euthanized, according to the recommendations of RN 37 of 02/22/2018 of CONCEA.[29] Next, the skin of the dorsal region was collected and packed in 10% formalin for the preparation of a histopathological slide.

EVALUATION OF THE ANTI-EDEMATOGENIC ACTIVITY OF F1 ON TIBIOTARSAL EDEMA IN A MODEL OF ARTHRITIS INDUCED BY MONOSODIUM URATE (MSU) CRYSTALS IN RATS.

The experimental model of gouty arthritis is widely used in the evaluation of new molecules with anti-inflammatory activity.[30] To carry out this protocol, 32 male Wistar rats were used, distributed in four groups consisting of 8 animals. Afterwards, the crystals of monosodium urate (uric acid) were diluted in 0.9% saline (40 mg/mL). Edema was induced on the 1st day of the experiment by injection in the tibiotarsal region with 100 µL of MSU in the right hind leg. The animals were pretreated with polaxamer gel and the F1 formulation at doses of 5 and 10 mg/kg (t.v.), Piroxicam 5 mg/kg (t.v.), 30 minutes before the injection of MSU. The treatment was repeated daily for a period of four days.

Revista ARACÊ
ISSN: 2358-2472

In this trial, the incidence and severity of arthritis were evaluated by measuring the volume of the right rear tibiotarsal region with a caliper (Pantec®) at times 0, 4, 24, 48 and 72 hours, 30 minutes after daily treatment with F1.[31]

EVALUATION OF THE ANTI-EDEMATOGENIC ACTIVITY OF THE F1 FORMULATION ON CARRAGEENAN-INDUCED PAW EDEMA IN RATS.

A total of 40 Wistar rats were used, distributed in 5 groups of 8 animals, and were pretreated transdermally (t.v.) with polaxamer gel (negative control), F1 at doses of 0.25, 0.50, 1 mg/kg, and Piroxicam (positive control) at a dose of 5.0 mg/kg (t.v.), 30 minutes before intraplantar administration (i.pl.) of carrageenan (1%; 0.1 mL) on the right hind leg. The formulation was lightly rubbed 50 times with the index finger.[32,33] The thickness of the paw was recorded by a digital caliper (Pantec®) at different times (1, 2, 3, 4 and 5 h) after carrageenan administration. Edema was expressed by the difference, in millimeters (mm), between the final and initial thickness of the paw.[34]

EVALUATION OF THE ANTI-EDEMATOGENIC ACTIVITY OF FORMULATIONS F1 AND F2 ON HISTAMINE-INDUCED PAW EDEMA IN RATS.

Initially, 32 male Wistar rats were divided into 4 groups of eight 8 animals followed by pre-treatments (v.t.) with polaxamer gel, F1 and F2 at a dose of 0.50 mg/kg, and Piroxicam 0.50 mg/kg (positive control). After 30 minutes, 100 µL of histamine (1%) was administered (i.pl.) to the right hind leg, the groups were treated with F1 and F2 only at a dose of 0.50 mg/kg (best effective dose). The thickness of the legs was recorded by a digital caliper (Pantec®), immediately before the administration of the phlogistic agent (t0) and every 30 minutes for an interval of up to 2 hours.

EVALUATION OF THE ANTI-EDEMATOGENIC ACTIVITY OF FORMULATIONS F1 AND F2 ON PROSTAGLANDIN-INDUCED PAW EDEMA IN RATS.

At first, 32 Wistar rats were divided into four groups each with eight 8 animals and pretreated (v.t.) with polaxamer gel, F1 and F2 at a dose of 0.50 mg/kg, and Piroxicam 0.50 mg/kg (positive control). After 30 minutes, 100 µL of prostaglandin (0.01%) was administered (i.pl.) to the right hind leg, the groups were treated with F1 and F2 only at a dose of 0.50 mg/kg (best effective dose). The thickness of the legs was recorded by a

Revista ARACÊ
ISSN: 2358-2472

digital caliper (Pantec®), immediately before the administration of the phlogistic agent (t0) and every 30 minutes for an interval of up to 2 hours.

EVALUATION OF THE ANTI-EDEMATOGENIC ACTIVITY OF FORMULATIONS F1 AND F2 ON ZYMOSAN-INDUCED TIBIOTARSAL JOINT EDEMA (ZY) IN RATS

In this protocol, 32 male Wistar rats, divided into four groups composed of eight animals, were previously submitted to light anesthesia with 30 µl of 2% lidocaine in the tibiotarsal joint. Arthritis was then induced with the administration of zy (1 mg/animal; 50µl) dissolved in saline solution in the right posterior knee joint. Subsequently, the analyzes were carried out for up to 6 hours. The animal groups were pretreated with formulations F1 (piroxicam emulgel) and F2 (bacuri butter emulgel) at doses of 0.5 mg/kg and positive and negative controls

Initially, the variation of edema in the right knee joint was evaluated, in which zy was injected using a digital caliper (Pantec®) to measure edema. The measurement was performed immediately before zy administration (T0) and subsequently every hour for six hours. To measure the joints, the animal was carefully immobilized and the measurement of the knee diameter was performed by the researcher. The edema was expressed in millimeters (mm). The data are presented as the difference between the values of the joint diameter obtained at T0 and every hour after zy administration.

STATISTICAL ANALYSIS OF THE RESULTS

The values were expressed as mean +/- standard deviation from the mean. The results obtained were submitted to analysis of variance (ANOVA), followed by Tukey's post-test, with the aid of the statistical software GraphPad Prism 6.0 (GraphPad Software, San Diego, CA, USA), and the values were considered significantly different when $p < 0.05$.

RESULTS

TECHNOLOGICAL ACHIEVEMENT AND EVALUATION OF THE PRELIMINARY STABILITY OF TOPICAL FORMULATIONS OF BACURI BUTTER AND PIROXICAM (F1) AND TOPICAL FORMULATION OF BACURI BUTTER (F2).

The formulations were adequate for evaluating activity in topical treatment in experimental arthritis. Therefore, the following tests were performed: tests to determine the organoleptic characteristics (pH, spreadability and organoleptic characteristics) before and

Revista ARACÊ
ISSN: 2358-2472

after the evaluation of the thermodynamic stability. As well as the validation of the piroxicam quantification method in the F1 formulation, for this purpose, it is presented: selective, linear, exact, precise and robust. The *in vitro release test* in a closed diffusion system as well as the other tests conducted in these formulations are approved according to RDC, 166 and RDC 318.[20.21]

EVALUATION OF THE ANTI-ARTHRITIC ACTIVITY OF BACURI AND PIROXICAM (F1) BUTTER FORMULATIONS AND BACURI BUTTER FORMULATION (F2) IN EXPERIMENTAL ARTHRITIS.

Table 02. Body weight of female rats during acute toxicity assessment, Teresina, PI, Brazil, 2024. (n=12).

Dose 2000mg/kg (v.t.)	Body weight in (g)		
	Day 0	Day 7	Day 14
Gel polaxamer	220.7±5.03	175.3±4.16**	212.7±4.04*
F1	193.7±4.93	208.0±5.56*	205.0±6.24
F2	194.7±6.65	232.7±0.57***	220.3±7.76**
MBP	255.3±10.79	266.0±5.56	277.3±14.74

Legend: Mean body weight of Wistar rats before (day 0), after 7 and 14 days of administration of polaxamer gel, (F1): topical formulation of bacuri butter and piroxicam, (F2): topical formulation of bacuri butter, (MBP): bacuri butter raw material transdermally (t.v.) (single dose). The values are expressed as mean ± SD *p<0.05, **p<0.01 and ***p<0.001 VS vehicle (one-way ANOVA followed by Tukey's post-test

The results show the absence of signs of systemic toxicity after the administration of the respective formulations (vehicle, F1, F2 and MBP) at a dose of 2000 mg/kg transdermally (t.v.). No animal deaths were observed during the observation time. Significant weight gain was observed in the animals when compared to the beginning of the protocol (Table 02). No behavioral changes were observed in the animals, since they did not present vocal frening, contortions, changes in the righting reflex. There were no changes in corneal reflexes, no tremors, convulsions, lacrimation, urination, defecation, piloerection, and cyanosis were identified during the 14-day observation period.

EVALUATION OF THE ANTIEDEMATOGENIC ACTIVITY OF THE F1 FORMULATION IN A MODEL OF ARTHRITIS INDUCED BY MONOSODIUM URATE (MSU) CRYSTALS IN RATS.

The administration of F1 at doses of 5 and 10 mg/kg (t.v.) as pre-treatment obtained a significant reduction ($p < 0.05$) of edema induced by monosodium urate crystals in rats in the tibiotarsal region after 24 hours of pre-treatment and was maintained for 72 hours of

Revista ARACÊ
ISSN: 2358-2472

observation when compared to animals that received only the vehicle (polaxamer gel). The mean inhibitions for the 5 mg/kg dose were 0.95 ± 0.61, 0.57 ± 0.29 and 0.42 ± 0.09, equivalent to 57.96, 76.54 and 79.61%, respectively. However, the animals pretreated with the dose of 10 mg/kg exhibited inhibition averages of 1.10 ± 0.17, 0.57 ± 0.33 and 0.65 ± 0.53, in that order. In percentage terms, it is equivalent to 51.32, 76.54 and 68.44% of tibiotarsal edema. The reference drug at a dose of 5 mg/kg significantly inhibited ($p < 0.05$) the formation of edema also from the second reading (24 h) and lasted for the entire observation period, compared to the vehicle group. During the first reading, it was evidenced that only the animals pretreated with the 5 mg/kg dose showed a significant decrease ($p < 0.05$) in edema (0.72 ± 0.26) when compared to the vehicle group (Table 3).

Table 03. Effect of the F1 formulation on uric acid-induced edema in the tibiotarsal region in rats, Teresina, PI, Brazil, 2024. (n=32)

Treatment (mg/kg, t.d.)	Joint volume variation (mm) Time Range (Hours)							
	4H	Inhibition (%)	24H	Inhibition (%)	48H	Inhibition (%)	72H	Inhibition (%)
Vehicle	1.53±0.56		2.26±0.49		2.43±0.37		2.06±0.11	
F1 (5)	0.72±0.26*	52,94	0.95±0.61*	57,96	0.57±0.29***	76,54	0.42±0.09***	79,61
F1 (10)	0.82±0.15	46,40	1.10±0.17*	51,32	0.57±0.33***	76,54	0.65±0.53***	68,44
Piroxicam (5)	0.83±015	45.75	0.93±0.20*	58,85	1.03±0.05***	57,61	0.50±0.20***	75,72
NOTE: Effect of F1 at doses of 5.10 mg/kg, (t.v.), vehicle, Piroxicam 5 mg/kg (t.v.) on uric acid-induced paw edema (40mg/mL) in the tibiotarsal region in rats. The values are expressed as mean ± SD *p<0.05 and ***p<0.001 VS vehicle (one-way ANOVA followed by Tukey's post-test								

Source: NPPM/UFPI

EVALUATION OF THE ANTI-EDEMATOGENIC ACTIVITY OF F1 ON CARRAGEENAN-INDUCED PAW EDEMA IN RATS.

The pre-treatment of the animals with the F1 formulation at doses of 0.25; 0.50 and 1 mg/kg (t.v.) significantly inhibited ($p < 0.05$) carrageenan-induced paw edema during the first hour of the evaluation, with mean inhibition of 2.10 ± 0.63; 1.31 ± 0.68 and 0.94 ± 0.69 when compared to the vehicle group, where a greater variation in edema was observed (3.30 ± 0.69). For the first hour of the analysis, the percentages of inhibition were respectively 36.36; 60.30 and 71.51%. For the second hour of analysis, the mean inhibition observed were 3.11 ± 0.55; 2.24 ± 0.87 and 1.73 ± 0.47, these data demonstrate a significant inhibition of edema in the groups pretreated with F1 at doses of 0.25, 0.50 and 1 mg/kg (t.v.), when compared to the vehicle group (5.24 ± 0.97).

The percentages of edema inhibition for this same time interval were 40.64; 57.25 and 66.98%. During the analysis of the third hour, significant inhibition ($p < 0.05$) of edema

Revista ARACÊ
ISSN: 2358-2472

was observed when compared to the vehicle group (5.93 ± 0.65), and the means found in this analysis were 3.53 ± 0.66, 2.47 ± 0.85 and 2.46 ± 0.45. The percentages of inhibition at the third hour were 40.47; 58.34 and 58.51%.

At the fourth hour, significant inhibition ($p < 0.05$) was also observed in the groups pretreated with F1 during the entire observation period, and the mean inhibition was 1.12 ± 0.58, respectively; 2.36 ± 0.82 and 2.00 ± 0.63. In percentage terms, edema was inhibited in up to 75.80; 49.02 and 56.80% in relation to the vehicle group for the same time interval. For the fifth hour of the analysis, significant inhibition of edema was also observed when compared to the vehicle group, with the measured means being 2.68 ± 0.49, respectively; 1.93 ± 0.65 and 1.115 ± 0.63, while the vehicle group had an average of 4.10 ± 0.44. In percentage, edema was reduced by 34.63; 52.92 and 71.95% for animals treated with F1.

Animals treated with piroxicam emulgel (positive control) at a dose of 5 mg/kg (t.v.) also showed significant inhibition ($p < 0.05$) of edema during the entire observation period, since the mean inhibition from the first to the fifth hour were 2.13 ± 1.10; 3.20 ± 0.53; 3.12 ± 0.37; 3.36 ± 0.43 and 3.12 ± 0.39. The percentages of inhibition for this same time interval were 35.45; 38,93, 47,38; 27.42 and 23.90% (Table 4).

Table 4: Effect of F1 on carrageenan-induced paw edema in rats. Teresina, PI, Brazil, 2024. (n=40)

Treatment (mg/Kg, v.t)	Shank volume variation (mm) Time Interval (Minutes) 1h	Inhibition (%)	2 hours	Inhibition (%)	3 hours	Inhibition (%)	4h	Inhibition (%)	5 hours	Inhibition (%)
Vehicle	3.30±0.69		5,240,97 ±		5.930.65±		4.63±0.43		4.10±0.44	
Piroxicam 0,25	2.10±0.63*	36,36	3,110,55 ****±	40,64	3,53 ±0,66 * ***	40,47	1.12±0.58***	75,80	2,68±0,49****	34,63
Piroxicam 0,5	1,31±0,68****	60,30	2,240,87 ****±	57,25	2,47 ±0,85 * ***	58,34	2,36±0,82****	49,02	1,93±0,65****	52,92
Piroxicam 1	0,94± 0.69****	71,51	1,73 ±0,47 ** **	66,98	2.46±0.45****	58,51	2,00±0,63****	56,80	1,15±0,63****	71,95
Piroxicam 5	2.13±1.10*	35,45	3,20 ±0,53 ** **	38,93	3.12±0.37****	47,38	3.36±0.43**	27,42	3.12±0.39**	23,90

Legend: Effect of F1 (0.25, 0.50 and 1 mg/kg, t.v.), vehicle, Piroxicam 5 mg/kg t.v.) on carrageenan-induced paw edema (1%; 0.1 mL, i.pl.) in rats. The values are expressed as mean ± SD, *p<0.05 **p<0.01 ***p<0.01 and ****p<0.001 the post-test ANOVA was applied onway followed by Tukey's post-test

Revista ARACÊ
ISSN: 2358-2472

EVALUATION OF THE ANTI-EDEMATOGENIC ACTIVITY OF FORMULATIONS F1 AND F2 ON HISTAMINE-INDUCED PAW EDEMA IN RATS

Administration of formulations F1 and F2 as pretreatment at a dose of 0.50 mg/kg (t.v.) significantly reduced ($p<0.05$) histamine-induced edema during the observation interval of up to 90 minutes when compared to the vehicle group. The mean inhibition evaluated for F1 at the intervals of 30, 60 and 90 minutes were 0.55±0.43, 0.56±0.41 and 0.45±0.30 respectively, in percentage terms equivalent to 66.86, 55.90 and 48.86%, in that order.

The group treated with the F2 formulation showed significantly decreased edema ($p<0.05$) when compared to the vehicle group, during the first 90 minutes, with inhibition averages of 0.89±0.39, 0.48±0.18 and 0.37±0.20 in that order. In percentage, this corresponds to 46.38, 62.20 and 57.95, respectively. Animals pre-treated with vehicle (t.v.) showed mean inhibition of 1.66±0.50; 1.27±0.59 and 0.88±0.29, in this group the variation in edema was described as 100% at all observation times. It is also worth noting that there was no significant inhibition of edema during the last reading at 120 minutes (Table 5).

Table 5. Effect of topical formulation of bacuri butter on paw edema of histamine and prostaglandin-induced wistar rats. Teresina, PI, Brazil, 2024. (n=32+32)

Treatment (mg/kg, v.t.)	Variation in the volume of histamine-induced paw edema (mm)							
	Time Interval (Minutes)							
	30 min	Inhibition (%)	60 min	Inhibition (%)	90 min	Inhibition (%)	120 min	Inhibition (%)
FP (vehicle)	1.66±0.50		1.27±0.59		0.88±0.29		0.42±0.27	
FMB (0,50)	0.89±0.39*	46,38	0.48±0.18**	62,20	0.37±0.20*	57,95	0.22±0.12	47,61
Piroxicam (5)	0.70±0.41**	57,38	0.59±0.27*	53,54	0.32±0.25*	63,63	0.12±0.11	71,42
Prostaglandin-induced paw edema volume variation (mm)								
Gel polaxamer	0.81±0.37		1.28±0.37		1.09±0.42		0.33±0.17	
FMB (0,50)	0.36±0.18*	55,55	0.64±0.22**	50,00	0.45±0.12**	58,71	0.41±0.23	24,24
Piroxicam (5)	0.31±0.5*	61,72	0.70±0.51*	45,31	0.57±028*	47,70	0.32±0.21	3,03

Legend: FP – polaxamer formulation, FMB – Bacuri butter formulation (0.50 mg/kg, t.v.), vehicle on histamine-induced paw edema (1%; 0.1 mL, i.pl.) in rats. The values are expressed as mean ± SD *p<0.05 **p<0.01 VS vehicle (one-way ANOVA followed by Tukey's post-test.

Revista ARACÊ
ISSN: 2358-2472

EVALUATION OF THE ANTI-EDEMATOGENIC ACTIVITY OF FORMULATIONS F1 AND F2 ON PROSTAGLANDIN-INDUCED PAW EDEMA IN RATS

Transdermal administration of formulations F1 and F2 as pretreatment at a dose of 0.5 mg/kg significantly inhibited ($p<0.05$) prostaglandin-induced edema (0.01%) in the right hind leg for up to 90 minutes of observation in relation to the vehicle group. The mean inhibition for the F1 formulation was 0.27±0.16; 0.52±0.28 and 0.46±0.25. The F2 formulation showed inhibition averages of 0.36±0.18; 0.64±0.22 and 0.45±0.12 mm. The standard drug used in this protocol showed antiedematogenic activity during the first 90 minutes of observation when compared to the vehicle group, with inhibition averages of 0.31±0.5, 0.70±0.51 and 0.57±028 mm, respectively. The vehicle group had averages of 0.81±0.37, 1.28±0.37; 1.09±0.42 and 0.33±0.17. In the last observation time (120 minutes), no significant inhibition of edema was observed in the groups pretreated with formulations F1 and F2 (Table 6).

EVALUATION OF THE ANTI-EDEMATOGENIC ACTIVITY OF FORMULATIONS F1 AND F2 ON ZYMOSAN-INDUCED TIBIOTARSAL JOINT EDEMA (ZY) IN RATS

Previous administration of F1 (0.50 mg/kg t.w.) showed a significant reduction ($p<0.05$) in edema compared to the vehicle group in the Zymosan model of arthritis. The mean inhibition presented for the F1 formulation were 0.50±0.21, 0.54±0.26, 0.35±0.21, 0.31±0.16 and 0.16±0.10 mm in relation to the vehicle group. These averages are equivalent to inhibitions of 42.52, 7.57, 66.01, 56.94 and 67.34%. On the other hand, the animals pretreated with the F2 formulation at a dose of 0.5 mg/kg did not show significant inhibition ($p>0.05$). Similarly, the group treated with piroxicam 5 mg/kg (positive control) also showed a decrease in edema during the first five evaluations, the mean inhibition presented were 0.38±0.16; 0.52±0.39; 0.26±0.22; 0.28±0.21; 0.14±0.07 and 0.

Table 6 - Evaluation of the effect of formulations F1 and F2 on paw edema induced by zymosan in rats. Teresina, PI, Brazil, 2024. (n=32)

Treatment (Mg/kg/t.d)	Paw volume variation											
	Intervalo de tempo											
	1h	Inhibition (%)	2 hours	Inhibition (%)	3 hours	Inhibition (%)	4h	Inhibition (%)	5 hours	Inhibition (%)	6 hours	Inhibition (%)
Vehicle	0.87±0.33	-	1.03±0.26		1.03±0.41		0.72±0.30		0.49±0.43		0.50±0.38	
F1(0,5)	0.50±0.21	42,52	0.54±0.26*	47,57	0.35±0.21**	66,01	0.31±0.16*	56,94	0.16±0.10*	67,34	0.19±0.22	62,00

Revista ARACÊ
ISSN: 2358-2472

F2(0,5)	0.56± 0.28	35, 63	0.55± 0.27	46,6 0	0.57±0. 40	44,6 6	0.47±0. 30	34,7 2	0.18±0 .08	63,2 6	0.34±0 .13	32,0 0
Piroxic am (5)	0.38± 0.16*	56, 32	0.52± 0.39*	49,5 1	0.26±0. 22***	74,7 5	0.28±0. 21**	61,1 1	0.14±0 .07*	71,4 2	0.27±0 .18	46,0 0
Note: Legend: Effect of the F1 and F2 formulation (0.50 mg/kg, t.v.), vehicle on zymosan-induced paw edema (0.01%; 0.1 mL, i.pl.) in rats. The values are expressed as mean ± SD *p<0.05 **p<0.01 and ***p<0.001 VS vehicle (one-way ANOVA followed by Tukey's post-test												

DISCUSSION

Corroborating this research, it was observed in the study entitled "Preclinical trials in rats treated with 1,3-diestearyl-2-oleylglycerol, an isolated constituent of *Platonia insignis*", in which they found that the acute treatment with this compound at a dose of 30 $^{mg.kg-1}$ did not alter in general the behavioral pattern of the rats and did not produce hematological and histopathological changes in the brain and liver areas analyzed.[35]

Still related to acute toxicity was detected in the named study: Preclinical toxicology of garcinielliptone FC, a tautomeric pair of polyprenylated benzophenone, isolated from seeds *of Platonia insignis* Mart, that treatment with garcinielliptone FC, at selected doses administered orally and intraperitoneally, showed relatively low risk of toxicity in all test animals, suggesting that it is safe for further investigation.[36]

Research related to the pharmacological activities of bacuri butter (Platonia insignis has shown actions such as: antioxidant, wound healing, leishmanicides and anticonvulsant activities through extracts extracted from bacuri butter.[37] Furthermore, the tea from the seeds of the fruit is empirically used in episodes of diarrhea.[38] In addition, the oil and yellow latex from the seeds are applied in cases of accidents with ophidians and some species of arachnids, topical treatment of skin conditions, otitis, rheumatism and arthritis due to their healing, antitumor, antimicrobial, antioxidant and cytotoxic qualities.[38.39]

Extracts and some compounds existing in the seeds of the bacuri have manifested anti-inflammatory, antioxidant, anticonvulsant and cytotoxic qualities, which are widely researched for the formulation of a possible drug that has pharmacological properties now identified, with therapeutic action against several diseases, such as cancer, Alzheimer's and Parkinson's disease.[40]

Studies have shown the antioxidant potential of *Platonia insignis* , which favors the fight against free radicals, which are normally implicated in mechanisms that induce inflammatory processes and pain (due to apoptosis).[40] It is believed that high levels of Reactive Oxygen Species (ROS) in the body can also lead to the manifestation of acute

Revista ARACÊ
ISSN: 2358-2472

pain.[41,42] However, studies that better clarify the mechanism of action of these effects are still fundamentally required by the small amount of material justifying these results.

In the research, "Antioxidant and anti-inflammatory effect of methanol extracts of *Asphodelus microcarpus*", whose purpose was to evaluate in vitro *pharmacological activity* of the different methanol extracts of *Asphodelus microcarpus*: leaf, stem, flowers and root, there was proof of pharmacological activity,43 such as those observed in the butter of the seed of *Platonia insignis.*

It was also possible to verify that in chemical studies attributed to the genus *Platonia*, several biologically active natural products were discovered, as well as xanthones and phloroglucinol derivatives, which constitute the elementary class of highly successful secondary metabolites of the Clusiaceae family. These derivatives have been widely examined due to their biological activities, integrating antioxidant, anti-inflammatory, cytotoxic and antimicrobial, antidepressant, anti-HIV, antitumor and antioxidant action39.

Histamine-induced paw edema is a classic model widely used in experiments involving edematogenic action.[44] It can bind basically to four G protein-coupled receptor subtypes (HR1, HR2, HR3, and HR4), which can favor the formation of phosphatidyl inositol (IP3), and consequently, increase intracellular calcium levels, and promote the activation of nuclear transcription factors, such as NF-κB. The HR1 and HR2 receptor subtypes are involved in most histamine-induced inflammatory responses.[45] Histamine is responsible for several vascular modifications, such as vasodilation, increased vascular permeability, favors platelet activating factor (FAP) synthesis and prostacyclin synthesis (PGI2).[46] Regarding the results obtained, both F1 and F2 showed antiedematogenic activity. Thus, it is possible to suggest that the formulations may interfere with the binding of histamine to its receptors, or even, as previously mentioned, inhibit histamine exocytosis in the interstitial medium.

Also corroborating the results obtained, it was noticed that the formulation of bacuri butter plus piroxicam (F1) as well as the formulation of bacuri butter alone (F2) significantly regressed the paw edema in rats induced by histamine, the results indicated that the analgesic action of the formulations was stronger than the anti-inflammatory action.[37]

In a complementary study, it was found that turmeric longa and *Zingiber officinalle* were the most pointed out as medicinal plants with anti-inflammatory action, used in the treatment of arthritis. Other plants with therapeutic potentials such as *Caesalpinia ferrea*; *Curcuma longa*; *Kalanchoe pinnata*; *Schinus terebinthifolius*; *Tabebuia avellanedae*;

Revista ARACÊ
ISSN: 2358-2472

Trifolium pratense; *Uncaria tomentosa*; *Zingiber officinale*, showed anti-inflammatory activities perhaps as did *Platonia insignis* Mart.[47] Research has revealed the ability of medicinal plant derivatives to selectively inhibit COX-2 activity in different edematogenic models using different phlogistic agents.[48,49] However, the anti-inflammatory activity may be associated with the presence of compounds such as: polyphenols, flavonoids, terpenoids, alkaloids, anthraquinones, lignins, polysaccharides, saponins and peptides, some of which are components in the seed of *Platonia insignis* Mart.[50.51]

The activity of formulations F1 and F2 in a prostaglandin-induced model of paw edema (PGE2) was also evaluated. PGE2 is considered a key pro-inflammatory mediator in the inflammatory process, being found in high levels in inflammatory exudates and when administered directly to the tissue, it is capable of inducing a series of classic signs of inflammation52. It is an abundant metabolite and plays an important role in the genesis of hyperalgesia, pyrexia and vascular permeability, being an important pharmacological target in inflammatory diseases.[53]

Since it modulates vascular events and favors the formation of exudate late, a few hours after the beginning of the inflammatory process, mainly potentiated by the effect of histamine, causing changes in its sensitivity, lowering the pain threshold for mediators such as histamine, serotonin and kinins, causing local pain, induced by mechanical and chemical agents, become more pronounced.[54]

PGE2 is produced by the degradation of arachidonic acid by cyclooxygenases, and released after its synthesis, it performs its biological function by activating the G protein-coupled receptor (EP). The heterogeneity in the biological functions of PGE2 is attributed to its binding to at least four different subtypes of EP receptors, which in turn express their signals through alteration of intracellular calcium (Ca2+) or modifications of cyclic adenosine-monophosphate (cAMP) levels.[55] Thus, PGE2 is responsible for the activation of several kinases that modulate a series of cellular functions, which can lead to an inflammatory response characterized by plasma leakage, pain, and fever.[56]

The study demonstrated that the F1 and F2 formulations showed antiedematogenic activity on PGE2-induced paw edema. This inhibitory activity may be related to inhibition of the PGE receptor or even block points in the PGE2-induced signaling pathway.

The Ben-Cha-Moon-Yai (BMY) remedy used in traditional Thai medicine as an anti-inflammatory, analgesic and antipyretic composed of five herbal root extracts with equal measures: Aegle quinces, Oroxylum indicum, Dimocarpus longan, Dolichandrone serrulata

Revista ARACÊ
ISSN: 2358-2472

and Walsura trichostemon Miq. These extracts exhibited anti-inflammatory properties, which may be due to their activity in the prostaglandin system57. Information observed in the formulations presented here (Table 6).

Research has revealed that *Allium cepa* L. (Liliaceae), the popular onion, is consumed all over the world. The substances that make up onions, including saponins, aglycones, quercetin, cepaenes, flavonoids, organosulfurs, and phenolic compounds, have shown various pharmacological properties and therapeutic effects. The results of the use of onion derivatives in oxidative stress, inflammatory and immune system were exhibited pointing out their therapeutic importance in the treatment of several diseases related to oxidative stress, inflammation and immune dysregulation.[58] Similar pharmacological activities were observed with the derivatives of the seed of Platonia insignis.

Next, the activity of the F1 formulation on Zymosan-induced paw edema (zy) was evaluated. This experimental model of arthritis in rodents is widely used because it has similarities with joint diseases in humans. Usually there is leukocyte infiltration, edema formation, and acute histopathological changes.[59.60]

The release of pro-inflammatory cytokines such as TNF-α, IL-18, IL-1β and IL-6, hypertrophy of the synovial joint and neutrophil recruitment are also observed. Neutrophils are the main cells present in the synovial fluid of joints with arthritis, they are often found near areas of cartilage erosion, favoring the formation of damage to cartilage tissue and bone matrix. This ends up favoring the release of oxidizing substances and protease enzymes, contributing to the progression of the disease.[61,62] Increased release of ROS, enzymes with high cartilage destructive power, is also common, which culminates in intense pain in the joints and some important socioeconomic limitations, especially in locomotion and work capacity. This occurs mainly in the presence of neutrophil infiltration in the joint region.[63,64,65]

These inflammatory conditions are similarly observed in the acute phase of rheumatoid arthritis and osteoarthritis. Therefore, intra-articular administration of Zymosan is an experimental model that promotes inflammatory parameters similar to RA.[66] It is a polysaccharide extracted from the wall of the fungus Saccharomyces cerevisiae,67 and is recognized by selectin-1 receptors, expressed in monocytes, macrophages, neutrophils and dendritic cells.[68]

Revista ARACÊ
ISSN: 2358-2472

After its recognition by macrophages, Zymosan interacts with the toll-like receptor (TLR2) on the surface of cells and induces the activation of the NF-kB factor, favoring the production of inflammatory cytokines.[69.70]

Quercetin is the flavonoid quite common in nature and exposes prominent antioxidant properties, encompassing oxygen radical scavenging, lipid peroxidation reduction, and metal ion chelation. Indicators show that quercetin inhibits the expression of pro-inflammatory cytokines (e.g., TNF-α) by eliminating NF-κB signaling ((nuclear factor kappa B) decreases paw edema and hyperalgesia, prevents attenuation of GSH (glutathione) levels caused by inflammatory agents, and decreases neutrophil recruitment by interdicting cell signaling responsible for actin polymerization71. In addition, quercetin precisely prevents the proliferation of synoviocytes and angiogenesis in an inflammatory process related to arthritis, showing its potential as an antirheumatic drug. Considering the evidence described here, the effects of quercetin were investigated in experimental zymosan-induced arthritis in mice with a focus on molecular events regulated by the transcription factors NF-κB and Nrf2(erythroid-derived nuclear factor 2).[71] Answers similar to those obtained in this study.

In a Zymosan-induced model of arthritis, in which pequi oil was used as a pretreatment in rats, it was observed that there was inhibition of the production of pro-inflammatory cytokines (TNF-α and IL-Iβ). Apparently, this action may be involved with the inhibition of neutrophil migration, with responses similar to those found in this study.[72]

In conclusion, it was evidenced that in the pre-treatment with bacuri butter emulgel and Piroxicam (F1) at doses of 5 and 10mg/kg (t.v.) in arthritis induced by monosodium urate crystals in rats in the tibiotarsal region, with evaluation of edema after 24h and 72h, it was detected that there was a reduction in edema when compared to the vehicle. But the dose of greatest statistical significance was 5 mg/kg.

In the pre-treatment with bacuri butter emulgel and Piroxicam (F1) in carrageenan-induced paw edema in rats at doses of 0.25; 0.5 and 1 mg/kg (t.v.) with evaluations from the 1st to the 5th h, a statistically significant reduction in edema was reported at the time intervals according to the arthritis protocol for all doses when compared with vehicle (Poloxamer gel) and positive control (Piroxicam gel).

In the pre-treatment with bacuri butter emulgel and Piroxicam (F1) and bacuri butter emulgel (F2), both at a dose of 5 mg/kg (t.v) in histamine-induced paw edema in rats, it was observed that there was involution of the edema in the times of 30 to 90 minutes when

Revista ARACÊ
ISSN: 2358-2472

compared to the vehicle.

In the pre-treatment with bacuri butter emulgel and piroxicam (F1) and bacuri butter emulgel both at a dose of 0.5 mg/kg (t.v.) in prostaglandin-induced paw edema in rats, it was observed that there was inhibitory activity of the edema activity that may be associated with PGE receptor inhibition.

In the pre-treatment with bacuri butter emulgel and Piroxicam (F1) in tibiotarsal edema induced by Zymosan in rats at a dose of 0.5 mg/kg (t.v.), in the evaluation of edema in the period from 1h to 6h, inhibition of edema was detected when confronted with the positive control (Piroxicam gel 0.5%) at a dose of 5 mg/kg (t.v.) and vehicle. As for the F2 formulation, it showed slight inhibition when compared to the vehicle, a situation expected in view of the action of F1, which showed superior efficacy to the commercialized Piroxicam.

CONCLUSION

According to the results obtained, it was possible to conclude that, to date, there is no commercially registered topical bacuri/piroxicam emulgel. Although patent registration No. BR 10202302227849, entitled; "Topical emulgel of bacuri butter (*Platonia Insignis* Mart.) for the treatment of arthritis", an integral part of this article was recently published in the INPI journal. The formulations did not show dermal toxicity and have antiarthritic activity proven in preclinical trials. Piroxicam emulgel showed superior activity to marketed piroxicam.

The formulations exhibited a potential associative effect with great pharmacological efficacy for the topical use of arthritis, especially in the elderly, given the amount of oral medications used by this clientele, which is exposed to the side effects of oral NSAIDs. This formulation has pleasant organoleptic characteristics and, as it is a product originating from medicinal plants, it is easy to access, in addition to excellent adhesion, spreadability and delivery of the active ingredient of the drug at the site of pain.

Revista ARACÊ
ISSN: 2358-2472

REFERENCES

1. Brophy, R. H., & Fillingham, Y. A. (2022). AAOS clinical practice guideline summary: Management of osteoarthritis of the knee (nonarthroplasty), third edition. The Journal of the American Academy of Orthopaedic Surgeons, 30(9), e721–e729. https://doi.org/10.5435/jaaos-d-21-01233

2. Rezende, M. U., Campos, G. C., & Pailo, A. F. (2013). Conceitos atuais em osteoartrite. Acta Ortopédica Brasileira, 21(2), 120–122. https://doi.org/10.1590/S1413-78522013000200010

3. American Academy of Orthopaedic Surgeons. (2021). Management of osteoarthritis of the knee (non-arthroplasty): Evidence-based clinical practice guideline. Rosemont: AAOS. Available at https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf

4. Mihalko, S. L., Cox, P., & Beavers, D. P. et al. (2018). Effect of intensive diet and exercise on self-efficacy in overweight and obese adults with knee osteoarthritis: The IDEA randomized clinical trial. Translational Behavioral Medicine, 9(2), 227-235. https://doi.org/10.1093/tbm/iby037

5. Miller, G. D., Nicklas, B. J., & Davis, C. et al. (2006). Intensive weight loss program improves physical function in older obese adults with knee osteoarthritis. Obesity (Silver Spring), 14(7), 1219-1230. https://doi.org/10.1038/oby.2006.139

6. Yilmaz, M., Sahin, M., & Algun, Z. C. (2019). Comparison of effectiveness of the home exercise program and the home exercise program taught by physiotherapist in knee osteoarthritis. Journal of Back and Musculoskeletal Rehabilitation, 32(1), 161-169. https://doi.org/10.3233/bmr-181234

7. Pan, S. Y., Zhou, S. F., & Gao, S. H. et al. (2013). New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. Evidence-Based Complementary and Alternative Medicine, 2013, Article ID 627375. https://doi.org/10.1155/2013/627375

8. Dias, D. A., Urban, S., & Roessner, U. (2012). A historical overview of natural products in drug discovery. Metabolites, 2(2), 303-336. https://doi.org/10.3390/metabo2020303

9. Aguiar, L. P., Figueredo, R. W., & Alves, R. E. et al. (2008). Physical and physico-chemical characterization of fruits from different genotypes of bacuri (Platonia insignis Mart.). Food Science and Technology, 28(2), 423-428. https://doi.org/10.1590/S0101-20612008000200024

10. Santos Jr, R. Q., Soares, L. C., & Maia Filho, A. L. M. et al. (2010). Estudo histológico da cicatrização de feridas cutâneas utilizando a banha de bacuri (Platonia insignis Mart.). ConScientiae Saúde, 9(4), 575-581. https://doi.org/10.5585/conssaude.v9i4.2357

Revista ARACÊ
ISSN: 2358-2472

11. Costa Jr, J. S., Feitosa, C. M., & Citó, A. M. G. L. et al. (2010). Evaluation of effects of ethanolic extract (EE) from Platonia insignis Mart. on pilocarpine-induced seizures. Journal of Biological Sciences, 10(8), 747-753. https://doi.org/10.3923/jbs.2010.747.753

12. Rufino, M. S. M., Alves, R. E., & Brito, E. S. et al. (2010). Bioactive compounds and antioxidant capacities of 18 non-traditional tropical fruits from Brazil. Food Chemistry, 121(4), 996-1002. https://doi.org/10.1016/j.foodchem.2010.01.037

13. Silva, P., Silva, M. P., & Oliveira, C. G. et al. (2015). Garcinielliptone FC: Antiparasitic activity without cytotoxicity to mammalian cells. Toxicology in Vitro, 29(4), 681-687. https://doi.org/10.1016/j.tiv.2014.12.014

14. Coelho, V. R., Prado, L. S., & Rossato, R. R. et al. (2018). A 28-day sub-acute genotoxic and behavioural assessment of garcinielliptone FC. Basic & Clinical Pharmacology & Toxicology, 123(2), 207-212. https://doi.org/10.1111/bcpt.13010

15. Cavalcante, N., Feitosa, C. M., & Santos, F. P. S. et al. (2019). Elaboration and characterization of the inclusion complex between β-cyclodextrin and the anticholinesterase 2-oleyl-1, 3-dipalmitoyl-glycerol extracted from the seeds of Platonia insignis Mart. Journal of Molecular Structure, 1177, 286-301. https://doi.org/10.1016/j.molstruc.2018.09.067

16. Freitas, F. A., Araújo, R. C., & Soares, E. R. et al. (2018). Biological evaluation and quantitative analysis of antioxidant compounds in pulps of the Amazonian fruits bacuri (Platonia insignis Mart.), ingá (Inga edulis Mart.), and uchi (Sacoglottis uchi Huber) by UHPLC-ESI-MS/MS. Journal of Food Biochemistry, 42(1), Article ID e12455. https://doi.org/10.1111/jfbc.12455

17. Bilanda, D. C., Dimo, T., & Djomeni, P. D. D. et al. (2010). Antihypertensive and antioxidant effects of Allanblackia floribunda Oliv. (Clusiaceae) aqueous extract in alcohol-and sucrose-induced hypertensive rats. Journal of Ethnopharmacology, 128(3), 634-640. https://doi.org/10.1016/j.jep.2010.02.025

18. Arcanjo, D. D. R., Costa-Júnior, J. S., & Moura, L. H. P. et al. (2014). Garcinielliptone FC, a polyisoprenylated benzophenone from Platonia insignis Mart., promotes vasorelaxant effect on rat mesenteric artery. Natural Product Research, 28(12), 923-927. https://doi.org/10.1080/14786419.2014.889136

19. Mendes, M. C. S., Oliveira, G. A. L., & Lacerda, J. S. et al. (2015). Evaluation of the cicatrizant activity of a semisolid pharmaceutical formulation obtained from Platonia insignis Mart. African Journal of Pharmacy and Pharmacology, 9(6), 154-164. https://doi.org/10.5897/AJPP2014.4169

20. Brasil, Ministério da Saúde, Agência Nacional de Vigilância Sanitária. (2017). Resolução da Diretoria Colegiada-RDC nº 166. Brasília: Ministério da Saúde.

Revista ARACÊ
ISSN: 2358-2472

21. Brasil, Ministério da Saúde. (2019). Resolução da Diretoria Colegiada: RDC, nº 318, de 6 de novembro de 2019: Establishes the criteria for conducting stability studies of active pharmaceutical ingredients and medications, except biologicals, and provides other provisions. Brasília: Ministério da Saúde.

22. OECD principles of corporate governance. (2004). Paris: OECD Publications.

23. Banerjee, S., Chattopadhyay, P., & Ghosh, A. et al. (2013). Acute dermal irritation, sensitization, and acute toxicity studies of a transdermal patch for prophylaxis against (+/-) anatoxin-a poisoning. International Journal of Toxicology, 32(4), 308–313. https://doi.org/10.1177/1091581813489996

24. Subota, V., Mirkov, I., & Demenesku, J. et al. (2016). Transdermal toxicity of topically applied anticoagulant rodenticide warfarin in rats. Environmental Toxicology and Pharmacology, 41, 232–240. https://doi.org/10.1016/j.etap.2015.12.006

25. Eroğlu, İ., Azizoğlu, E., & Özyazici, M. et al. (2016). Effective topical delivery systems for corticosteroids: Dermatological and histological evaluations. Drug Delivery, 23(5), 1502–1513. https://doi.org/10.3109/10717544.2014.960981

26. Ugwah-Oguejiofor, C. J., Okoli, C. O., & Ugwah, M. O. et al. (2019). Acute and sub-acute toxicity of aqueous extract of aerial parts of Caralluma dalzielii NE Brown in mice and rats. Heliyon, 5(1), Article ID e01179. https://doi.org/10.1016/j.heliyon.2019.e01179

27. Antonio, C. B., Costa, T. D., & Neves, G. et al. (2009). Métodos de transposição de doses obtidas em farmacologia pré-clinica para ensaios clínicos fase 1: Antipsicóticos como estudo de caso. Latin American Journal of Pharmacy, 28(5), 715-722. http://www.latamjpharm.org/resumenes/28/5/LAJOP_28_5_1_11.pdf

28. Reigner, B. G., & Blesch, K. (2002). Estimating the starting dose for entry into humans: Principles and practice. European Journal of Clinical Pharmacology, 57(12), 835-845. https://doi.org/10.1007/s00228-001-0405-6

29. Preuss, S. et al. (2018). Impacto da criação da CEUA/UFSC e do Conselho Nacional de Controle de Experimentação Animal (CONCEA) sobre o número de animais utilizado para pesquisa na UFSC. Florianópolis: UFSC.

30. Rasool, M., & Varalakshmi, P. (2006). Immunomodulatory role of Withania somnifera root powder on experimental induced inflammation: An in vivo and in vitro study. Vascular Pharmacology, 44(6), 406–410. https://doi.org/10.1016/j.vph.2006.01.015

31. Valentin, E. E., Teixeira, S. A., & Muscará, M. N. (2008). Efeito protetor do sulfeto de hidrogênio na artrite aguda induzida por carragenina. In Anais... Congresso do Instituto de Ciências Biomédicas da Universidade de São Paulo. Comissão de Cultura e Extensão Universitária do ICB/USP.

Revista ARACÊ
ISSN: 2358-2472

32. Calvo, M. I. (2006). Anti-inflammatory and analgesic activity of the topical preparation of Verbena officinalis L. Journal of Ethnopharmacology, 107(3), 380–382. https://doi.org/10.1016/j.jep.2006.03.037

33. MD, S., Alhakamy, N. A., & Aldawsari, H. M. et al. (2020). Improved analgesic and anti-inflammatory effect of diclofenac sodium by topical nanoemulgel: Formulation development - in vitro and in vivo studies. Journal of Chemistry, 2020, Article ID 4071818. https://doi.org/10.1155/2020/4071818

34. Winter, C. A., Risley, E. A., & Nuss, G. W. (1962). Carrageenin-induced edema in hind paw of the rat as an assay for antiinflammatory drugs. Experimental Biology and Medicine, 111(3), 544–547. https://doi.org/10.3181/00379727-111-27849

35. Feitosa, C. M., Santos, P. R. P., & Freitas, R. M. et al. (2015). Ensaios pré-clínicos em ratos tratados com 1, 3-diestearil-2-oleilglicerol, constituinte isolado de Platonia insignis. Conscientiae Saúde, 14(4), 555–567. https://doi.org/10.5585/conssaude.v14n4.5658

36. Silva, L. S., & Cruz, F. S. F. (2015). Anti-inflamatórios não esteroidais: Não seletivos ou seletivos, qual o melhor? In Salão do Conhecimento.

37. Ribeiro, J. F., Figueiredo, M. L. F., & Carvalho, A. L. M. et al. (2021). Pharmacological actions of bacuri butter (Platonia insignis Mart.): An integrative review. Revista Rene, 22, Article ID e59963. https://doi.org/10.15253/2175-6783.20212259963

38. Costa Jr, J. S., Ferraz, A. B. F., & Filho, B. A. B. et al. (2011). Evaluation of antioxidant effects in vitro of garcinielliptone FC (GFC) isolated from Platonia insignis. Journal of Medicinal Plants Research, 5(2), 293-299. https://doi.org/10.5897/JMPR.9000617

39. Costa Jr, J. S., Almeida, A. A. C., & Ferraz, A. B. F. et al. (2013). Cytotoxic and leishmanicidal properties of garcinielliptone FC, a prenylated benzophenone from Platonia insignis. Natural Product Research, 27(4-5), 470-474. https://doi.org/10.1080/14786419.2012.695363

40. Santos, G. P. (2014). Potencial antioxidante, análise de açúcares e ácidos orgânicos em polpas in natura, polpas liofilizadas e farinhas de acerola (Malpighia emarginata), graviola (Annona muricata L.) e mangaba (Hancornia speciosa). (Dissertation, Mestrado em Ciência e Tecnologia de Alimentos) - Universidade Federal de Sergipe, São Cristóvão.

41. Fidanboylu, M., Griffiths, L. A., & Flatters, S. J. L. (2011). Global inhibition of reactive oxygen species (ROS) inhibits paclitaxel-induced painful peripheral neuropathy. PloS One, 6(9), Article ID e25212. https://doi.org/10.1371/journal.pone.0025212

42. Yowtak, J., Lee, K. Y., & Kim, H. Y. et al. (2011). Reactive oxygen species contribute to neuropathic pain by reducing spinal GABA release. Pain, 152(4), 844-852. https://doi.org/10.1016/j.pain.2010.12.034

Revista ARACÊ
ISSN: 2358-2472

43. Mayouf, N., Charef, N., & Saoudi, S. et al. (2019). Antioxidant and anti-inflammatory effect of Asphodelus microcarpus methanolic extracts. Journal of Ethnopharmacology, 239, Article ID 111914. https://doi.org/10.1016/j.jep.2019.111914

44. Tamaddonfard, E., Farshid, A. A., & Hosseini, L. (2012). Crocin alleviates the local paw edema induced by histamine in rats. Avicenna Journal of Phytomedicine, 2(2), 97–104. https://pubmed.ncbi.nlm.nih.gov/25050237/

45. Jutel, M., Akdis, M., & Akdis, C. A. (2009). Histamine, histamine receptors and their role in immune pathology. Clinical & Experimental Allergy, 39(12), 1786-1800. https://doi.org/10.1111/j.1365-2222.2009.03374.x

46. Riedl, A., Schlederer, M., & Pudelko, K. et al. (2017). Comparison of cancer cells in 2D vs 3D culture reveals differences in AKT–mTOR–S6K signaling and drug responses. Journal of Cell Science, 130(1), 203-218. https://doi.org/10.1242/jcs.188102

47. Marmitt, D. J., Rempel, C., & Goettert, M. I. et al. (2015). Plantas medicinais da RENISUS com potencial anti-inflamatório: Revisão sistemática em três bases de dados científicas. Revista Fitos, 9(2), 129-144. https://doi.org/10.5935/2446-4775.20150011

48. Castelo, K. F. A. et al. (2018). Estudo químico dos extratos ativos de bacuri (Platonia insignis). (Dissertation, Mestrado em Química) - Universidade Federal do Amazonas, Manaus.

49. van Breemen, R. B., Tao, Y., & Li, W. (2011). Cyclooxygenase-2 inhibitors in ginger (Zingiber officinale). Fitoterapia, 82(1), 38-43. https://doi.org/10.1016/j.fitote.2010.09.004

50. Sparg, S. G., Light, M. E., & van Staden, J. (2004). Biological activities and distribution of plant saponins. Journal of Ethnopharmacology, 94(2-3), 219-243. https://doi.org/10.1016/j.jep.2004.05.016

51. Zhonglin, W., Lei, C., & Kit-Tai, H. et al. (2004). Testing and application of the mediating effects. Acta Psychologica Sinica, 36(5), 614-620. https://journal.psych.ac.cn/acps/EN/abstract/abstract2852.shtml

52. Claudino, R. F. (2006). Caracterização farmacológica e molecular dos mecanismos envolvidos no edema de pata induzido pela prostaglandina E2 (PGE2) em camundongos. (Dissertation, Mestrado em Farmacologia) - Universidade Federal de Santa Catarina, Florianópolis, Santa Catarina.

53. Rashid, T., & Seligman, M. (2019). Psicoterapia positiva: manual do terapeuta. Artmed Editora.

54. Poluha, R. L., & Grossmann, E. (2018). Mediadores inflamatórios relacionados às disfunções temporomandibulares artrogênicas. BrJP, 1(1), 60-65. https://doi.org/10.5935/2595-0118.20180013

Revista ARACÊ
ISSN: 2358-2472

55. Dewitt, D. L. (1991). Prostaglandin endoperoxide synthase: Regulation of enzyme expression. Biochimica et Biophysica Acta, 1083(2), 121-134. https://doi.org/10.1016/0005-2760(91)90032-D

56. Dey, M., Lejeune, F., & Chadee, K. (2006). Prostaglandin E2 receptor distribution and function in the gastrointestinal tract. British Journal of Pharmacology, 149(6), 611-623. https://doi.org/10.1038/sj.bjp.0706923

57. Kiratipaiboon, C., Wanasa, P. W. D., Hasriadi, A., et al. (2022). Herbal root extracts in Ben-Cha-Moon-Yai remedy attenuated pain-like behaviors and inflammation through the opioid and prostaglandin systems. Journal of Ethnopharmacology, 290, Article ID 115088. https://doi.org/10.1016/j.jep.2022.115088

58. Marefati, N., Ghorani, V., Shakeri, F., et al. (2021). A review of anti-inflammatory, antioxidant, and immunomodulatory effects of Allium cepa and its main constituents. Pharmaceutical Biology, 59(1), 285-300. https://doi.org/10.1080/13880209.2021.1874028

59. Cash, J. L., White, G. E., & Greaves, D. R. (2009). Zymosan-induced peritonitis as a simple experimental system for the study of inflammation. Methods in Enzymology, 461, 379-396. https://doi.org/10.1016/S0076-6879(09)05417-2

60. Dolati, M., Rezaei, K., Vanak, Z. P., et al. (2016). Study of the effects of essential oils of cumin, savory and cardamom as natural antioxidants on the flavor and oxidative stability of soybean oil during the storage. Journal of Essential Oil Bearing Plants, 19(1), 176-184. https://doi.org/10.1080/0972060X.2014.935030

61. Bardoel, B. W., Kenny, E. F., Sollberger, G., et al. (2014). The balancing act of neutrophils. Cell Host & Microbe, 15(5), 526–536. https://doi.org/10.1016/j.chom.2014.04.011

62. Németh, T., & Mócsai, A. (2012). The role of neutrophils in autoimmune diseases. Immunology Letters, 143(1), 9-19. https://doi.org/10.1016/j.imlet.2012.01.013

63. Cascão, R., Rósario, H. S., Souto-Carneiro, M. M., et al. (2010). Neutrophils in rheumatoid arthritis: More than simple final effectors. Autoimmunity Reviews, 9(8), 531-535. https://doi.org/10.1016/j.autrev.2009.12.013

64. Burska, A., Hunt, L., Boissinot, M., et al. (2014). Autoantibodies to posttranslational modifications in rheumatoid arthritis. Mediators of Inflammation, 2014, Article ID 492873. https://doi.org/10.1155/2014/492873

65. Kundu, J. K., & Young-Joon, S. (2012). Emerging avenues linking inflammation and cancer. Free Radical Biology and Medicine, 52(9), 2013-2037. https://doi.org/10.1016/j.freeradbiomed.2012.02.035

66. Guazelli, C. F. S., Staurengo-Ferrari, L., Zarpelon, A. C., et al. (2018). Quercetin attenuates zymosan-induced arthritis in mice. Biomedicine & Pharmacotherapy, 102, 175-184. https://doi.org/10.1016/j.biopha.2018.03.057

Revista ARACÊ
ISSN: 2358-2472

67. Bringel, P. H. S. F., Marques, G. F. O., Martins, M. G. Q., et al. (2020). The lectin isolated from the alga Hypnea cervicornis promotes antinociception in rats subjected to zymosan-induced arthritis: Involvement of cGMP signalization and cytokine expression. Inflammation, 43(4), 1446-1454. https://doi.org/10.1007/s10753-020-01222-z

68. Willment, J. A., Lin, H. H., Reid, D. M., et al. (2003). Dectin-1 expression and function are enhanced on alternatively activated and GM-CSF-treated macrophages and are negatively regulated by IL-10, dexamethasone, and lipopolysaccharide. The Journal of Immunology, 171(9), 4569-4573. https://doi.org/10.4049/jimmunol.171.9.4569

69. Taylor, P. R., Brown, G. D., Reid, D. M., et al. (2002). The β-glucan receptor, dectin-1, is predominantly expressed on the surface of cells of the monocyte/macrophage and neutrophil lineages. The Journal of Immunology, 169(7), 3876-3882. https://doi.org/10.4049/jimmunol.169.7.3876

70. Zarpelon, A. C., Pinto, L. G., Cunha, T. M., et al. (2012). Endothelin-1 induces neutrophil recruitment in adaptive inflammation via TNFα and CXCL1/CXCR2 in mice. Canadian Journal of Physiology and Pharmacology, 90(2), 187-199. https://doi.org/10.1139/y11-116

71. Oliveira, F. F. B. (2015). Efeito antinociceptivo e anti-inflamatório do óleo da polpa de pequi Caryocar coriaceum Wittm na artrite induzida por zymosan em ratos. (Dissertation, Mestrado em Farmacologia) – Universidade Federal do Ceará, Fortaleza (CE).