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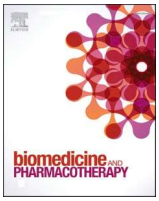

Evaluation of the antiedematogenic and anti-inflammatory properties of *Ximenia americana* L. (Olacaceae) bark extract in experimental models of inflammation

Bruno Anderson Fernandes da Silva [a,b], Renata Torres Pessoa [c], Roger Henrique Sousa da Costa [c], Maria Rayane Correia de Oliveira [c], Andreza Guedes Barbosa Ramos [c], Maria Gabriely de Lima Silva [c], Lucas Yure Santos da Silva [c], Cassio Rocha Medeiros [d], Sloana Giesta Lemos Florencio [d], Jaime Ribeiro-Filho [e], Henrique Douglas Melo Coutinho [f,*], António Raposo [g], Sunghoon Yoo [h,*], Heesup Han [i,*], Irwin Rose Alencar de Menezes [c], Lucindo José Quintans Júnior [a,b]

[a] *Laboratory of Neurosciences and Pharmacological Assays, Department of Physiology, Federal University of Sergipe, São Cristóvão, SE, Brazil*
[b] *Health Sciences Graduate Program, Federal University of Sergipe, Aracaju, SE, Brazil*
[c] *Laboratory of Pharmacology and Molecular Chemistry, Department of Biological Chemical, Regional University of Cariri, Cel Antonio Luis 1161, Pimenta, CEP 63105-000, Crato, CE, Brazil*
[d] *CECAPE College, Av. Padre Cícero, 3917 - São José, Juazeiro do Norte, CE 63024–015, Brazil*
[e] *Oswaldo Cruz Foundation, Fiocruz Ceará, Eusébio, CE 61773–270, Brazil*
[f] *Department of Biological Chemistry, Regional University of Cariri – URCA, Crato, CE 63105–000, Brazil*
[g] *CBIOS (Research Center for Biosciences and Health Technologies), Universidade Lusófona de Humanidades e Tecnologias, Campo Grande 376, 1749-024 Lisboa, Portugal*
[h] *Audit Team, Hanmoo Convention (Oakwood Premier), 49, Teheran-ro 87-gil, Gangnam-gu, Seoul 06164, South Korea*
[i] *College of Hospitality and Tourism Management, Sejong University, 98 Gunja-Dong, Gwanjin-Gu, Seoul 143-747, South Korea*

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ABSTRACT

Edema is one of the obvious indicators of inflammation and a crucial factor to take into account when assessing a substance's capacity to reduce inflammation. We aimed to evaluate the antiedematogenic and anti-inflammatory profile of the hydroethanolic barks extract of Ximenia americana (HEXA). The possible antiedematogenic and anti-inflammatory effect of EHXA (50, 100 mg/kg and 250 mg/kg v.o) was evaluated using the paw edema induced by carrageenan, zymosan, dextran, CFA and by different agents inflammatory (serotonin, histamine, arachidonic acid and PGE_2), and pleurisy model induced by carrageenan and its action on IL-1β and TNF-α levels was also evaluated. HEXA demonstrated a significant antiedematogenic effect at concentrations of 50, 100 and 250 mg/kg on paw edema induced by carrageenan, zymosan and dextran. However, the concentration of 50 mg/kg as standard, demonstrating the effect in the subchronic model, induced CFA with inhibition of 59.06 %. In models of histamine-induced paw edema, HEXA showed inhibition of – 30 min: 40.49 %, 60 min: 44.70 % and 90 min: 48.98 %; serotonin inhibition - 30 min: 57.09 %, 60 min: 66.04 % and 90 min: 61.79 %; arachidonic acid inhibition - 15 min: 36.54 %, 30 min: 51.10 %, 45 min: 50.32 % and 60 min: 76.17 %; and PGE_2 inhibition - 15 min: 67.78 %, 30 min: 62.30 %, 45 min: 54.25 % and 60 min: 47.92 %. HEXA significantly reduced ($p < 0.01$) leukocyte migration in the pleurisy model and reduced TNF-α and IL-1β levels in pleural lavage ($p < 0.0001$). The results showed that HEXA has the potential to have an antiedematogenic impact in both acute and chronic inflammation processes, with a putative mode of action including the suppression or regulation of inflammatory mediators.

* Corresponding authors.
E-mail addresses: hdmcoutinho@gmail.com (H.D.M. Coutinho), sunghoon@hmcon.co.kr (S. Yoo), heesup.han@gmail.com (H. Han).

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1. Introduction

Inflammation is the immune system's first line of defense against tissue injury, involving a complex cascade of cellular and vascular reactions that can be caused by numerous factors. These reactions have physiological functions that assist in the control and restoration of tissue to its normal state [1]. Edema is one of the classic signs of an inflammatory reaction followed by redness, fever and pain [2]. These symptoms are mediated by the release and increased concentration of cytokines such as interleukin 1-beta (IL-1β), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) [3] and prostaglandin E_2 (PGE_2) [4].

If the acute inflammatory response is not resolved, it can progress to a subchronic and/or chronic condition, which can result in pathologies including autoimmune diseases as arthritis, hormonal diseases as diabetes, respiratory diseases as asthma, atherosclerosis, and cancer [5]. Considering the side effects associated with anti-inflammatory drugs, there is a demand for medicinal plants with anti-inflammatory therapeutic effects with few or no side effects [6]. In the population of the Caatinga Biome, the medicinal use of natural plant-based products is common to complement or replace commercially manufactured herbal medicines. [7,8].

The genus *Ximenia* belongs to the Olacaceae family and comprises about eight species: *X. roiigi*, *X. aegyptica*, *X. parviflora*, *X. coriaceae*, *X. aculeata*, *X. caffra*, *X. aegyptica* and *X. americana* [9,10]. Some species of this genus, such as *X. americana* is used in folk medicine to treat inflammatory disorders and their anti-inflammatory activities have been evidenced [11]. *Ximenia americana* is the most studied species and has several anti-inflammatory properties [12–21].

Ximenia americana L. (Olacaceae) is a plant of great socioeconomic value because it can be used as food, source of essential oil, industrial component of other products and in folk medicine as a phytotherapic in the treatment of humans and animals [13]. Studies have shown that the species has gastroprotective [21], anticancer and antineoplastic [22], antimicrobial [23–26], pesticidal [27], analgesic [19,28,29], antiulcer [30], antirheumatic and antipyretic [19], acaricidal [31], antidiabetic [32,33], antiparasitic activity [34], anti-nociceptive [14,15], anti-inflammatory activity [14–16,18–20] and hepatic and hematological effects [35].

Thus, considering the therapeutic potential use of *Ximenia americana* L. in the treatment of inflammatory diseases, these study aims were proposed to characterize and evaluate the systemic antiedematogenic effect of the hydroethanolic extract of barks *X. americana* (HEXA) using acute and chronic models of paw edema induced by different inflammatory agents in mice.

2. Materials and methods

2.1. Plant material and extract preparation

The extract of barks of *Ximenia americana* L. (Oleaceae) was prepared according to previously published work by Silva et al. (2018). For this, the barks of *Ximenia americana* were collected at the "Sítio lambedor", in June 2014, located in the municipality of Farias Brito (Caatinga domain area), Ceará State, Brazil, under the geographic coordinates: SAD 69 - Latitude 06° 57 '2630'' and Longitude 39° 32 '1740''). Species voucher (number 10976) was deposited at the Herbarium Dárdano Andrade-Lima Caririense (HCDAL). The plant barks were dried and transferred to a container where they were soaked in a mixture of distilled water and absolute ethanol (1:1) for a period of 72 h. The hydroethanolic extract obtained from the husks of *X. americana* (HEXA) was filtered and then transferred to a rotary evaporator (27–35 rpm; 45 °C) for ethanol removal. After removing the solvent, the extract was kept in a water bath for ethanol evaporation and 24 h later it was frozen to finally be lyophilized. The chemical profile is determined by HPLC-DAD analysis identification of the presence of polyphenols Caffeic Acid, Elagic Acid and flavonoids catechin, quercitrin, rutin, and kaempferol were found in stem barks X. americana ethanolic extract.

2.2. Chemicals

Analytical grade chemicals were used in all experiments. Acetone and Ethanol Dynamics (Brazil). Dextran, Serotonin, Zymosan, PGE_2, Arachidonic acid, Complex Freunds Adjuvant (CFA), histamine Sigma Chemical Co. (St. Louis, MO, USA), IL-1β and TNF-α (eBioscience®).

2.3. Animals

Animals female and male mice (20–30 g) from the Bioterio of the Regional University of Cariri - URCA. All animals were maintained with food (Labina, Purina, Brazil) and water ad libitum in climatized temperature at 24 ± 2 °C and a light/dark cycle of 12 h. This study was carried out in accordance with the recommendations of the National Council for the Control of Animal Experiments (CONCEA) and Guide for the care and use of laboratory animals of National Institute of Health-USA (NIH, 1996), and the protocols were approved by the Animal Experimentation and Use Committee of URCA with process number CEUA Nº 82/2015 and 180/2020.2.

2.4. Carrageenan, zymosan and dextran-induced paw edema in mice

The plethysmometry method was used to evaluate the animals. The animals were divided into four groups (n = 6); saline solution and HEXA (50, 100 and 250 mg/kg doses). 60 min after pretreatment, the animals received 1 % (20 μL/paw) carrageenan [35] or 1 % zymosan (20 μL/paw) [36] in the paw right hind leg and vehicle on the left paw. The volume of the right hind paw of each animal was recorded after 60, 120, 180, 240 and 300 min for carrageenan, for zymosan 60 – 360 min of injection of inflammatory agent.

For dextran-induced edema the animals were divided into four groups (n = 6); saline and HEXA (50, 100 and 250 mg/kg). 60 min after pretreatment, the animals received 1 % dextran (20 μL/paw) in the right hind paw and vehicle in the left. The volume of the right hind paw of each animal was recorded after 30, 60, 90 and 120 min of the injection of inflammatory agent [37].

2.5. Histamine, serotonin, AA and PGE_2-induced paw edema in mice

Animals were pre-treated orally (p.o.) with saline and HEXA (50 mg/kg). After 1 h, the animals received 1 % arachidonic acid or 1 % histamine or 1 % serotonin in the right hind paw (20 μL/paw) and vehicle in the left paw. Paw volumes were measured at intervals of 15, 30, 45 and 60 min after AA injection [38] and PGE_2 injection. To assess histamine and serotonin-induced paw edema, the volume of the hind paw of each animal was recorded after 30, 60, 90 and 120 min of the injection of the inflammatory agents [39].

2.6. Complete Freund's Adjuvant (CFA)-induced subchronic paw edema in mice

The basal volume of the hind paws of each mouse were measured by plethysmometry. After 1 h, the animals received CFA (w/v) (20 μL/paw) in the right hind paw and in the left only an induction stimulus (without substance administration). Immediately after induction, they were treated with injectable water (Control: 0.01 mL/g v.o.) and either HEXA (50 mg/kg v.o.). The treatments were performed on the 5th, 9th, 13th, 17th and 21th. The volume of the right and left hind paw of each animal was recorded daily until the 21th day of injection of the inducing agent (CFA) [36,37].

2.7. Carrageenan-induced pleurisy in mice

Group of mice were subjected oral dose of HEXA (50 mg/kg)

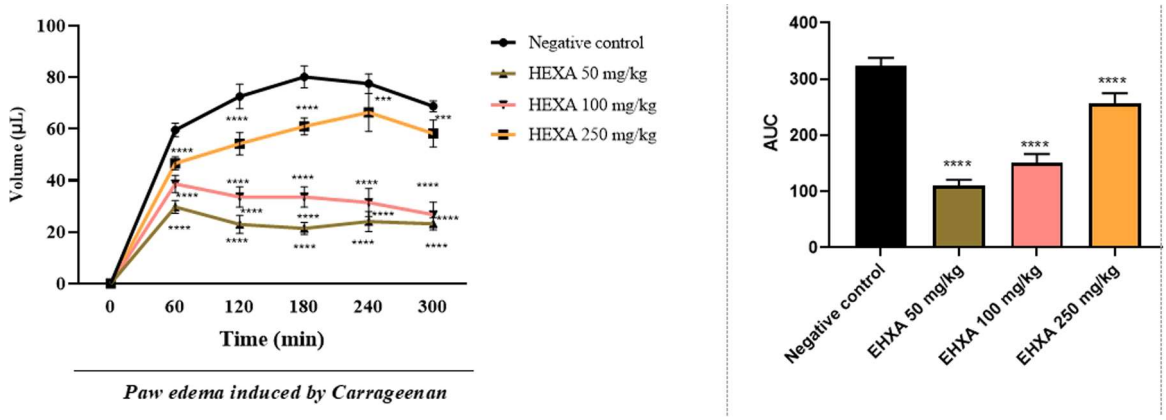

Fig. 1. Effect of HEXA on the carrageenan-induced paw edema model in mice. Negative control and HEXA (50, 100 and 250 mg/kg, p.o.) were administered 1 h before the injection of carrageenan in the intra-plantar region of the animals. The lines show the effect of HEXA (50, 100 and 250 mg/kg) in reducing edema from 60 min to 300 min after carrageenan injection. Columns represent S.D. means (n = 6 per group) in AUC. Statistical Analysis: Two-way ANOVA followed by Bonferroni's test. ***P < 0.001 and P* ** *< 0.0001 compared to the control group.

dissolved in distilled water and sham group also received distilled water. The negative control was given only distilled water, the same via 1 h before carrageenan pleural injection. Pleurisy was induced in the mice by intrapleural administration of 100 µL of 1 % (w/ v) carrageenan suspension in sterile saline solution. Sham group received saline. A specially adapted 13 × 5 needle was introduced into the right side of the thoracic cavity for injection of the carrageenan solution. Four hours after the induction of pleurisy, the animals were euthanized, and the pleural inflammatory exudate was collected through pleural lavage with 1 mL of phosphate buffered saline (PBS) containing ethylenediaminetetraacetic acid (EDTA; 10 mM). The pleural lavage was centrifuged (1500 rpm for 10 min at room temperature) and the precipitate was resuspended with 1 mL of PBS, and an aliquot of 50 µL was diluted with Turk's solution (1:20). The total leukocytes were counted in a Neubauer chamber, considering four external quadrants, using a light microscope [38]. The TNF-α and IL-1β levels in the supernatant of the centrifuged exudates were detected by ELISA using enzyme-linked immunosorbent assay (ELISA) kits (eBioscience®) according to the manufacturer's instructions. The colorimetric measurements at 450 nm were made in a microplate reader (ASYS®) and the concentrations were obtained by interpolation from a standard curve [39]. All results were expressed as picograms (pg) of cytokine per milliliter (mL).

2.8. Statistical analysis

The values are expressed as mean ± standard error of the mean (S.E.M) of six observations and evaluated by analysis of variance (ANOVA) using one-way and two-way trials, followed by Student-Newman-Keuls' or Bonferroni's tests. The statistical significance was considered with $p < 0.05$ for all analyzes using the Graph Pad Prism (9.0) software (San Diego, CA, USA).

3. Results and discussion

The literature showed that qualitative chemical prospecting indicated the presence of glycosides, cyanogenic glycosides, steroids, alkaloids, saponins, anthraquinones, flavonoids, terpenoids and tannins. Several compounds are isolated such as sambunigrin, gallic acid, catechin and different stereoisomers of (epi)catechin, gallotannins quercetin, quercetin-3-O-β-xylopyranoside, quercetin-3-O-(6″-galloyl)-β-glucopyranoside quercitrin, avicularin, β-glucogalin, 1,6-digalloyl-β-glucopyranose and kaempferol-3-O (6″-galloyl)-β-glucopyranoside [42,43]. We recently demonstrated that similar extract analysis by HPLC with chemical composition of rutin, gallic acid, quercetin, catechin, kaempferol, chlorogenic acid and ellagic acid, however, caffeic acid and quercitrin were quantified as main compounds [40].

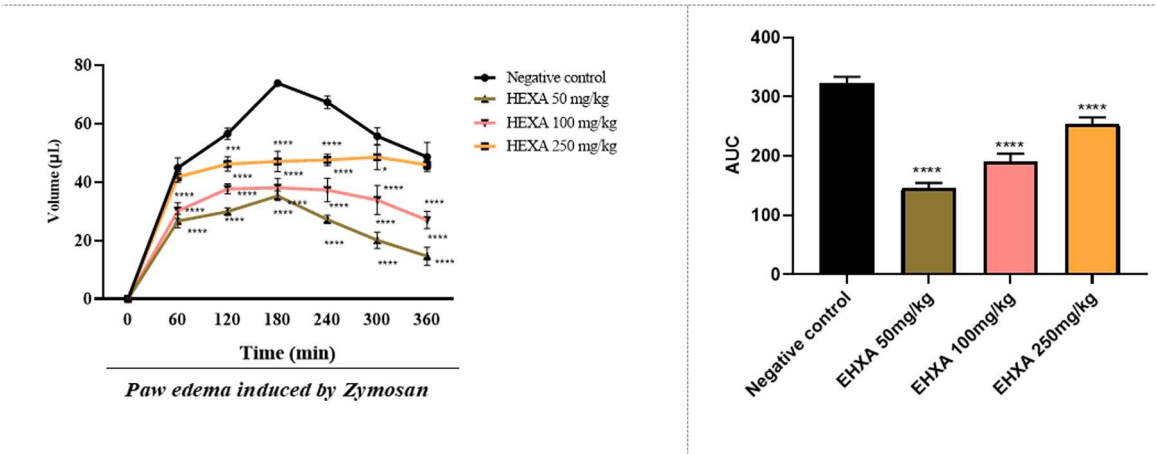

Fig. 2. Effect of HEXA on the zymosan-induced paw edema model in mice. Negative control and HEXA (50, 100 and 250 mg/kg, p.o.) were administered 1 h before the injection of carrageenan in the intra-plantar region of the animals. The lines show the effect of HEXA (50, 100 and 250 mg/kg) in reducing edema from 60 min to 360 min after zymosan injection. Columns represent S.D. means (n = 6 per group) in AUC. Statistical Analysis: Two-way ANOVA followed by Bonferroni's test. * P < 0.05, * **P < 0.001 and P * ** * < 0.0001 compared to the control group.

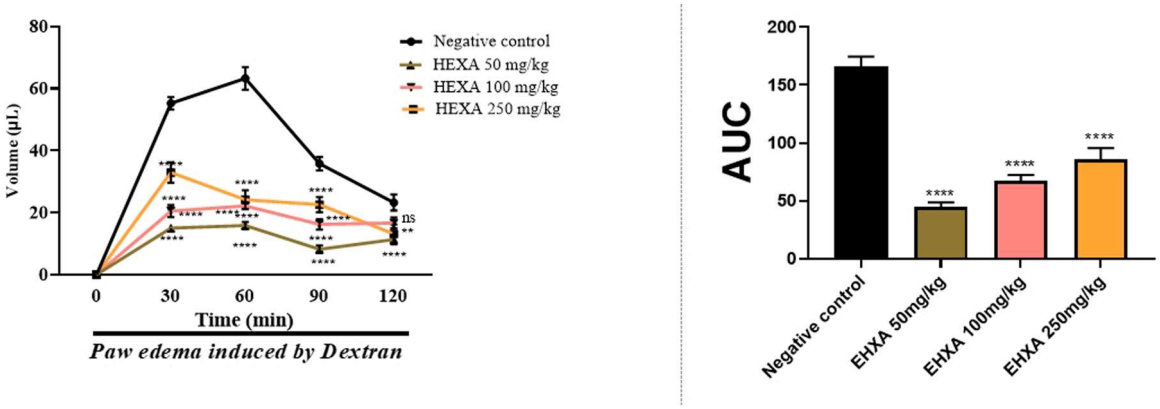

Fig. 3. Effect of HEXA on the dextran-induced paw edema model in mice. Negative control and HEXA (50, 100 and 250 mg/kg, p.o.) were administered 1 h before the injection of carrageenan in the intra-plantar region of the animals. The lines show the effect of HEXA (50, 100 and 250 mg/kg) in reducing edema from 30 min to 120 min after dextran injection. Columns represent S.D. means (n = 6 per group) in AUC. Statistical Analysis: Two-way ANOVA followed by Bonferroni's test. * *P < 0,01, * **P < 0.001 and P * ** *< 0.0001 compared to the control group.

Studies on the anti-inflammatory activity of *Ximenia americana* have been investigated in recent years through several studies in vitro and in vivo models demonstrating anti-inflammatory effects through various inflammation pathways, either by inhibiting or modulating arachidonic acid metabolites, vasoactive amines or involvement in decreasing levels of key inflammatory cytokines [11,14,15,17,18,20,21,28,41–44]. Silva et al. (2018) and De Menezes et al. (2019) presented the phytochemical analysis of the hydroethanolic extract of the bark of *X. americana* by HPLC. According to HPLC analysis, gallic acid [46], quercetin, quercitrin, catechin, rutin, kaempferol, chlorogenic acid, caffeic acid and ellagic acid were identified in HEXA [11,16,25,27,28,45,46]. Among these, quercitrin and caffeic acid were the main constituents and presented the highest concentrations [16].

To evaluate the systemic antiedematogenic effect of HEXA, *screening* of paw edema by carrageenan, zymosan, dextran and possible mechanisms of action involved through the edema of paw edema models induced by histamine, serotonin, arachidonic acid and PGE_2. In addition, the effect of HEXA on the subchronic inflammatory model induced by CFA was evaluated.

The sign of edema is one of the key features of acute inflammation [47]. Substances that promote the reduction of this parameter should be considered promising for the antiedematogenic search for new lead compounds with therapeutic responses [48–50]. Oral administration of HEXA significantly inhibited carrageenan (see Fig. 1), zymosan (see Fig. 2) and dextran (see Fig. 3) induced paw edema *screening*.

Carrageenan-induced paw edema is used to identify possible potential of non-steroidal anti-inflammatory compounds [51,52]. Carrageenan-induced inflammation is a biphasic model [55]. The initial phase (0–1 h) is characterized by the release of vasoactive amines, serotonin, histamine and kinins from mast cells [56–65]. The observed increase in vascular permeability and blood flow is mediated by vasodilation due to the release of autacoids (histamine and serotonin), which leads to the formation of edema [53]. The late phase (1–6 h) is mediated by leukotrienes, prostaglandins produced by tissue macrophages, nitric oxide (NO) and bradykinin (BK) within 3 h [54–64].

HEXA (50, 100 and 250 mg/kg) demonstrated an edema inhibitory effect (EIE) at all times evaluated when compared to the control group in the carrageenan model. The 50 mg/kg dose demonstrated EIE: 60 min: 50.13 %; 120 min: 68.53 %; 180 min: 73.31 %; 240 min: 68.96 % and 300 min: 66.25 %; 100 mg/kg demonstrated EIE: 60 min: 35.10 %; 120 min: 53.70 %; 180 min: 58.08 %; 240 min: 59.49 % and 300 min: 61.05 %; and 250 mg/kg demonstrated EIE: 60 min: 21.67 %; 120 min: 25.20 %; 180 min: 23.93 %; 240 min: 14.41 % and 300 min: 15.36 % (see Fig. 1); (Table S1).

The effects of extract *X. americana* on carrageenan-induced paw edema is widely studied in literature and corroborate our results. Onifade et al. (2011), Siddaiah et al. (2012) and Kimondo et al. (2020) showed similar results in reduction of paw edema at all evaluation times when compared to the control group [20,41,65]. According to Onifade et al., (2011) the extract inhibited the migration of neutrophils, leukocytes and reduced vascular permeability and suggested that the anti-inflammatory effect of the extract is due to its chemical characterization that revealed the presence of flavonoids, tannins, saponins, triterpenes and sterols, which corroborates our results.

Zymosan promote mast cell degranulation, activation of macrophages and the complement system, platelet activating factor (PAF), in addition to the release of PGs, NO [66,67] and cytokines (TNF-α, IL-1β and IL-6) [3,68–71]. The biochemical basis for inflammatory response by zymosan is multifactorial [72]. However, the β-glucan present in the zymosan complex promotes the activation of dectin-1 and Toll-like receptor-2 (TLR2), initiating pathophysiological responses by damage-associated molecular patterns (DAMPs) released late after tissue injury [73]. Plasma extravasation has chemotactic factors that will mediate the influx of leukocytes, leading to their accumulation in the inflamed tissue [2,59,74].

In zymosan-induced paw edema, HEXA (50 mg/kg and 100 mg/kg) demonstrated EIE at all times evaluated when compared to the control group. The 50 mg/kg dose demonstrated EIE: 60 min: 40.57 %; 120 min: 47.11 %; 180 min: 52.08 %; 240 min: 59.83 %; 300 min: 63.94 % and 360 min: 69.79 %; The 100 mg/kg dose demonstrated EIE: 60 min: 32.61 %; 120 min: 33.41 %; 180 min: 48.50 %; 240 min: 44.65 %; 300 min: 39.26 % and 360 min: 38.23 %. The dose of 250 mg/kg showed an inhibitory effect only at times of 120 min (EIE: 18.35 %); 180 min (EIE: 36.28 %); 240 min (EIE: 29.33 %) and 300 min (EIE: 48.50 %) when compared to the control group (see Fig. 2); (Table S2).

Dias et al., (2018) presented the effect of ethanol extract, ethyl acetate, and hydromethanol fraction of *X. americana* on zymosan-induced peritonitis [15]. According this study, the decrease in leukocyte recruitment attributed to *X. americana* is due to its possible ability to decrease the production of cytokines, which corroborates our results. However, dose of 250 mg/kg (HEXA), at the last evaluation time, didn't demonstrate edema inhibitory effect (EIE) when compared to control, the explanation for this behavior is possibly due to the inflammatory exudate followed by time-dependent recruitment on neutrophils [59,75–78].

Dextran causes a distinct inflammatory response in two phases. Initially (0–1 h) there is edema formation and increased vascular permeability triggered by the release of histamine. The second phase (1–6 h) has a predominance of serotonin, release of PGs, NO and cytokines [79]. Silva et al., (2018) demonstrate the effect of HEXA in the

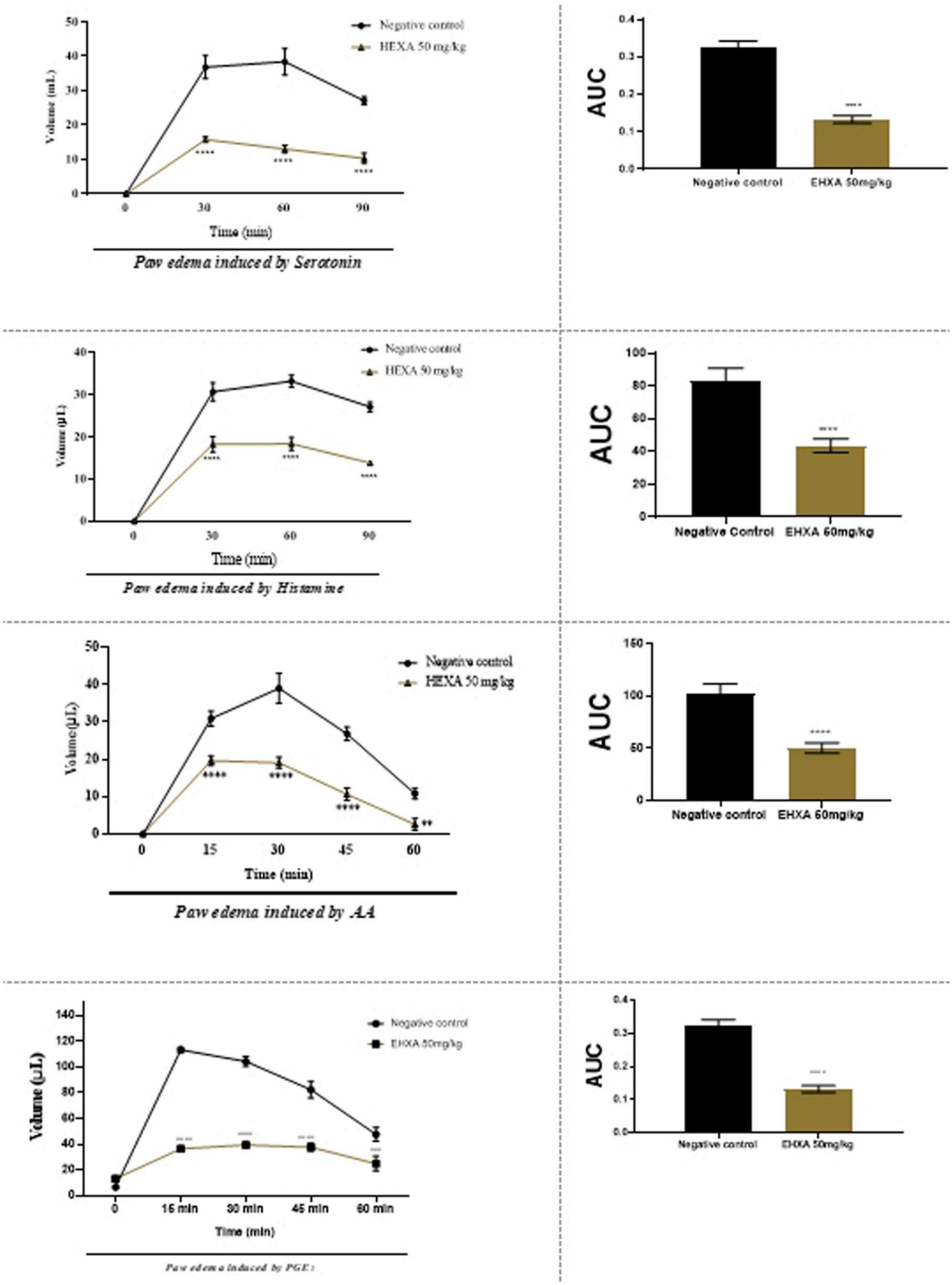

Fig. 4. Effect of HEXA on the paw edema model induced by serotonin, histamine, AA and PGE_2 in mice. Negative control and HEXA (50 mg/kg p.o.) were administered 1 h before the injection of carrageenan in the intra-plantar region of the animals. The lines show the effect of HEXA in reducing edema from 15 min to 90 min after injection. Columns represent S.D. means (n = 6 per group) in AUC. Statistical Analysis: Two-way ANOVA followed by Bonferroni's test. P * ** *< 0.0001 compared to the control group.

model of ear edema induced by intradermal histamine injection, which corroborates the initial results of dextran-induced paw edema. However, there are no reports in the literature about the effect of *X. americana* on serotonin, another mediator involved in the formation of edema. We confirmed the inhibition of autacoids and prostaglandins by *X. americana* using models of edema induced by histamine, serotonin, arachidonic acid and PGE_2. The systemic antiedematogenic effect attributed to the extract in this study can be explained by its chemical

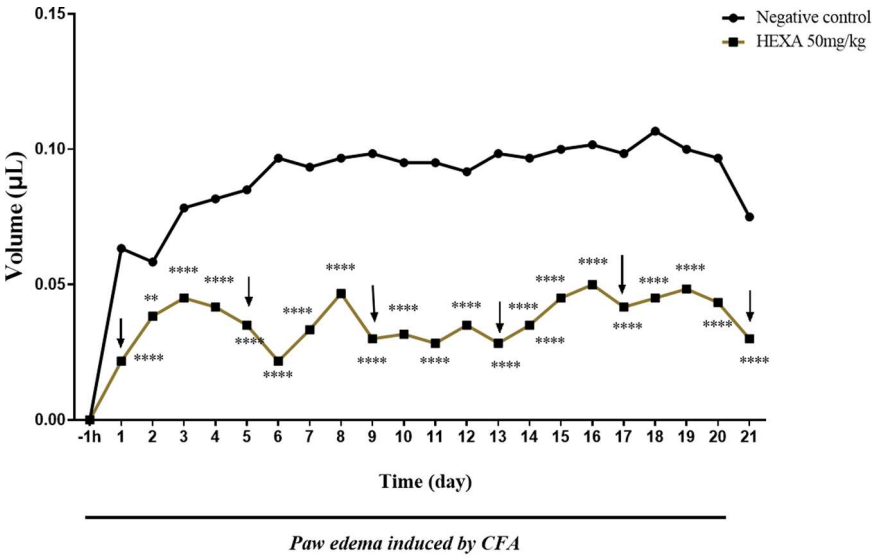

Fig. 5. Effect of HEXA on the CFA-induced subchronic paw edema model in mice. Negative control and HEXA (50 mg/kg p. o.) were administered 1 h before the injection of carrageenan in the intra-plantar region of the animals. Treatments were performed on days 5, 9, 13, 17 and 21 (The arrows indicate the treatment). The volume of the right and left hindpaw of each animal was recorded daily until the 21st day of the injection of the inducing agent (CFA). The lines show the effect of HEXA in reducing edema during the 21 days of evaluation after CFA injection. Statistical Analysis: Two-way ANOVA followed by Bonferroni's test (n = 6 per group). P * * < 0.01 and P * * * * < 0.0001 compared to the control group.

composition. Quercitrin and caffeic acid are the components with the highest concentrations present in HEXA, followed by quercetin and gallic acid [80,81].

HEXA was effective in dextran-induced paw edema at all evaluation times when compared to control. 50 mg/kg dose demonstrated EIE: 30 min: 72.88 %; 60 min: 74.96 %; 90 min: 77.10 % and 120 min: 51.33 %; 100 mg/kg demonstrated EIE: 30 min: 62.97 %; 60 min: 64.94 %; 90 min: 54.97 % and 120 min: 28.23 %; 250 mg/kg demonstrated EIE: 30 min: 40.43 %; 60 min: 61.82 %; 90 min: 36.94 % and 120 min: 43.42 % (see Fig. 3); (Table S3). Based on these results, the low dose was selected for evaluation of possible mechanism and subchronic effect.

Our results are in agreement with the activities presented for screening the topical antiedematogenic activity of HEXA suggested by Silva et al. (2018) that was able to reduce croton oil-induced ear edema (acute and chronic model) [80], whose oil action mechanism in the acute model involves the activation of several cellular and vascular events of the inflammatory process, resulting from the release of chemical mediators as: histamine, serotonin (5-HT), prostaglandin E_2, leukotrienes and various pro-inflammatory cytokines.

Taguchi et al., (1993) and Byung et al. (2007) demonstrated that quercitrin has a dose-dependent effect in reducing paw edema induced by carrageenan, dextran, histamine, serotonin and BK, and zymosan-induced paw edema[82,83]. Quercitrin is widely reported for its actions directly impacting the production of cytokines in the inflammatory process [84], reducing inflammatory cells [85], and inhibiting the nuclear factor kappa B (NF-kB) pathway and consequently the production of NO [86]. The inhibition of cytokines such as IL-1β, TNF-α, IL-6 by caffeic acid [87–92], quercetin [85,93–96] and gallic acid [97] can be related to the activities presented.

Histamine is an inflammatory mediator produced by mast cells that plays a role in cell signaling and in several physiological processes, including cells with immune functions, such as antigen-presenting cells (APCs), *natural killer* cells (NK) and T and B cells [98]. Therefore, after tissue injury or immune response, mast cells undergo degranulation releasing histamine from their interior into the bloodstream, causing increased blood flow and vascular permeability [99].

Serotonin (5-hydroxytryptamine or 5-HT) is another preformed vasoactive mediator with histamine-like actions [60]. 5-HT produces flushing, one of the characteristics of inflammation and the possible explanation for this fact is venous constriction with consequent increase in capillary filling [100]. The present study demonstrated that the administration of HEXA reduced the formation of paw edema in the histamine and serotonin model. In Fig. 4 it was shown that treatment with HEXA (50 mg/kg) significantly reduced histamine-induced paw edema (EIA: 30 min: 40.49 %; 60 min: 44.70 % and 90 min: 48.98 % %) (Table S4); and by serotonin (EIA: 30 min: 57.09 %; 60 min: 66.04 % and 90 min: 61.79 %) (Tab. S5) when compared to the control group. These inferences complemented the inhibition of paw edema induced by carrageenan (early phase), dextran and confirmed the inhibition of autacoids as one of the possible mechanisms (see Fig. 4).

The arachidonic acid (AA) pathway begins with the presence of a noxious stimulus that activates the enzyme phospholipase A_2, which in turn degrades membrane phospholipids and releases AA, which is then oxidized by the enzyme cyclooxygenase (COX) and lipoxygenase. (LOX), which results in the synthesis of prostaglandins (PGs), thromboxane's (TXs) via the COX pathway [101,102], leukotrienes (LTs)) and lipoxins (LXs) via the LOX pathway [103,104]. Prostaglandins are inflammatory mediators produced by arachidonic acid generated specifically by cyclooxygenase-2 (COX-2) [105,106] that cause vasodilation, release of other mediators and sensitization of nerve endings. Prostaglandin (PGE_2) is produced through the key enzyme COX-2, and is responsible for the increased production of prostaglandins at the inflamed site [4].

In Fig. 4 it was shown that treatment with HEXA (50 mg/kg) significantly reduced AA-induced paw edema (EIA: 15 min: 36.54 %; 30 min: 51.10 %; 45 min: 50.32 % and 60 min: 76.17 %) (Table S6); and PGE_2 EIE: 15 min: 67.78 %; 30 min: 62.30 %; 45 min: 54.25 % and 60 min: 47.92 %) (Table S7) when compared to the control group.

HEXA was also effective in reducing edema formation by AA and PGE_2 metabolites. These inferences complemented the inhibition of edema induced by carrageenan (second phase) and zymosan and confirmed the inhibition/decrease in the production of arachidonic acid or prostaglandin metabolites as one of the possible mechanisms (see Fig. 4c and d). The effect of HEXA on arachidonic acid was previously reported by Silva et al. (2018) through the AA-induced ear edema model. The results presented here corroborate the literature data and confirm the possible involvement of inhibition of the action of AA and PGE_2 metabolites.

Quercitrin is widely reported to inhibit COX-1, COX-2 and leukotrienes [107–110]. Certain flavonoids (eg quercetin) are high-affinity reducing co-substrates for COX-1 and COX-2 [111]. Because it is a glycoside formed from quercetin, quercetin may demonstrate a quercetin-like cyclooxygenase inhibition mechanism. Gallic acid can cause inhibition of COX-1 and AA-induced platelet function [112]. Caffeic acid and quercetin are 5-LOX inhibitors [113].

Silva et al. (2018) propose the possible topical antiedematogenic effect of HEXA by inhibiting PGE_2 production. In our study, we

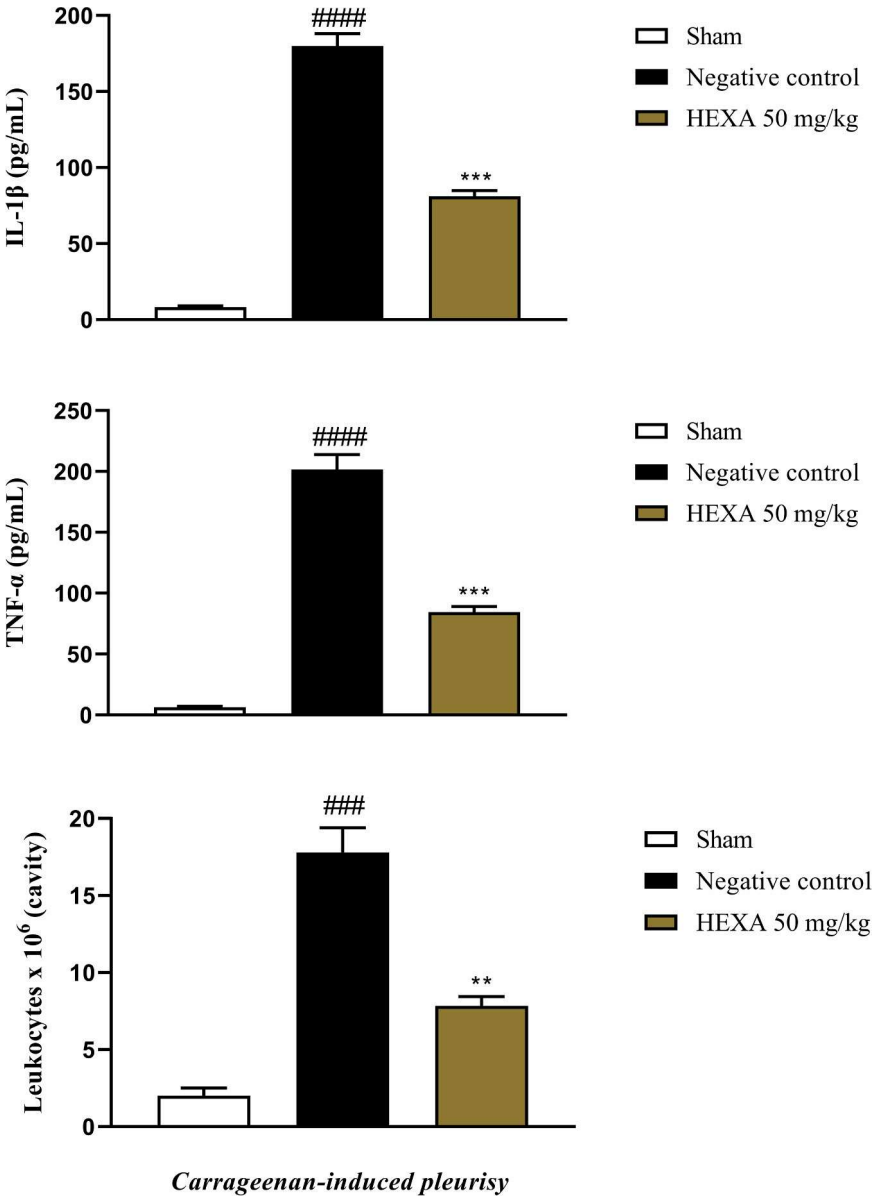

Fig. 6. Effect of HEXA on carrageenan induced pleurisy in mice. Distilled water (negative control and Sham) or HEXA (50 mg/kg p. o.) were administered 1 h before carrageenan injection. The analyses were performed 4 h after carrageenan injection to evaluate the recruitment of total leukocytes and the levels of IL-1β, TNF-α. Statistical Analysis: One-way ANOVA followed by Tukey's test (n = 6 per group). P ** < 0.01, P *** < 0.001 and P **** < 0.0001 compared to the negative control; ### P < 0.001 and #### P < 0.0001 vs sham groups.

corroborate the data present in the literature. Gallic acid [114], Quercitrin [107,115–117], caffeic acid [118–122] and quercetin [113] are reported to inhibit PGE_2 production.

Complete Freund's Adjuvant (CFA) triggers a local inflammatory process involving several mediators. The cytokines IL-1, IL-6 and TNF-α are detected at low concentrations in CFA-induced acute inflammation. However, during the chronic inflammatory process, these and other cytokines are present in high concentrations [36]. Together, cytokines can stimulate the production of chemokines, responsible for inducing the migration of lymphocytes and macrophages [3]. Injection of CFA into the hind paw of rodents induces a long-lasting inflammatory process, leading to mechanical and thermal allodynia, which can last for weeks [123].

Results from other studies in rodents have already shown that paw edema, evident throughout the evaluation period, is the result of vasodilation and increased vascular permeability involving kinins [124], with exudation of plasma proteins and fluid, as well as amplification of the resulting inflammatory mechanisms activation of precursors present in plasma [125].

Treatments with HEXA (50 mg/kg) significantly reduced the percentage of CFA-induced edema by 59.06 % when compared to the control group. As for the time intervals, treatment with HEXA showed EIA in 65.78 % (day 01), 34.29 % (day 02), 42.55 % (day 03), 48.64 % (day 04), 58.82 % (day 05), 77.58 % (day 06), 64.29 % (day 07), 51.72 % (day 08), 69.49 % (day 09), 66.66 % (day 10), 70.18 % (day 11), 61.82 % (day 12), 71.19 % (day 13), 63.79 % (day 14), 55 % (day 15), 50.83 % (day 16), 59.03 % (day 17), 57.82 % (day 18), 51.67 % (day 19), 55.18 % (day 20), 60 % (day 21), respectively, when compared to the control group (see Fig. 5).

HEXA reduced CFA-induced edema (subchronic model) when compared to the control group (see Fig. 5), which corroborates the results found by Silva et al. (2018) in the croton oil-induced ear edema model (chronic model), HEXA demonstrated a similar effect to dexamethasone (corticosteroid) [123]. Our findings suggest that the HEXA subchronic antiedematogenic activity is due, in part, to the inhibition of the action and/or synthesis of cytokines (IL-1β, TNF-α, IL-6), inhibition of PGE_2 and 5-LOX, which corroborates the results found by Silva et al. (2018).

Furthermore, the results presented here corroborate the data in the literature [109,111,126–129]. Quercitrin, caffeic acid, quercetin and gallic acid inhibit several pro-inflammatory cytokines, inhibit the arachidonic acid metabolite cascade pathway, prostaglandin pathway

and leukotriene pathway [107,112,114,119–121,127,130–134]. Previous studies have revealed that quercetin increases levels of pro-inflammatory cytokines such as IL-10 (immunoregulatory, anti-inflammatory and/or pro-inflammatory in the pathogenesis of rheumatoid arthritis) [135]. Our results and the compilation of information on the chemistry of HEXA demonstrate the efficacy of *Ximenia americana* L. in both acute and chronic systemic inflammatory processes.

During the inflammatory process, the concentration of pro-inflammatory cytokines such as IL-1β and TNF-α play a key role because their levels are high on the 2,3 and 4 h (see Fig. 6). Thus, in order to characterize the possible anti-inflammatory effect of HEXA, we verified whether the pre-treatment of the extract could have activity in reducing leukocyte infiltration using the carrageenan-induced pleurisy model in mice. This model is useful, as IL-1β plays a fundamental role in maintaining the accumulation of cells in the pleural cavity (cell influx), but not in the formation of edema (Scognamillo-Szabó et al., 2005). As expected, after carrageenan administration, the number of leukocytes in the pleural cavity increased significantly ($p < 0.001$) compared to the Sham group. We demonstrated that pretreatment with HEXA (50 mg/kg, p.o.) reduced the number of leukocytes ($p < 0.01$) compared to the negative control (Fig. 6). These results corroborate previous studies that demonstrated that the *X. americana* extract is capable of inhibiting leukocyte migration in models of peritonitis induced by carrageenan and zymosan, according to Onifande et al. (2011) and Dias et al. (2018), effects that may be associated with the ability to decrease cytokine levels.

In order to explain how some of the main cytokines of the inflammatory process may be affected by pretreatment with HEXA, we investigated the levels of cytokines in pleural exudates in the model of pleurisy induced by carrageenan. The levels of IL-1β and TNF-α in the supernatant of centrifuged exudates were evaluated by ELISA assay. It was shown that IL-1β and TNF-α levels increased significantly ($p < 0.0001$) in the supernatant of centrifuged exudates after carrageenan injection. However, pre-treatment with HEXA was able to significantly reduce ($p < 0.001$) the levels of IL-1β and TNF-α in the pleural exudate compared to the vehicle group (Fig. 2B and C). TNF-α is a very important pro-inflammatory cytokine that induces several other cytokines in the pro-inflammatory cascade, including IL-1β, IL-6, IL-8 and granulocyte macrophage colony stimulating factor (GM-CSF) and its modulation has been the target for the study of promising new chemical entities for the control of chronic inflammation [38,39,136].

Togheter, these results suggest that the effect of HEXA in the reduction of PGE2 edema may be contribute to the anti-exudative activities of anti-inflammatory action in carrageenin pleurisy. Also suggest that prostaglandin E2 could be a regulating factor involved in cytokine production at the inflammatory site by increase in nuclear factor-κB DNA binding activity paralleled both exudate formation and leukocyte infiltration [137]. These results corroborate data from the literature on the chemical constituents present in the extract of *X. americana* that had a direct effect on the production of cytokines, inhibiting the actions of IL-1β and TNF-α, effects that may be related to the presence of acid caffeic acid, quercetin, quercetin and gallic acid [86–97].

4. Conclusion

The results of this study suggest that HEXA was able to reduce paw edema induced by different inflammatory agents in acute and chronic models similar to the effect demonstrated by Silva et al. (2018), however, we demonstrated the anti-inflammatory effect of HEXA in the model of pleurisy induced by carrageenan and its actions on IL-1β and TNF-α levels. According to our results, the extract has possible mechanisms of action due to inhibition/modulation of autacoids (serotonin and histamine), cytokines (IL-1β, and TNF-α) and PGE_2. Therefore, EHXA is a possible natural product with anti-inflammatory pharmacological value to be used in the study and development of new herbal medicines and/or products for the treatment of inflammatory processes.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2023.115249.

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