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Effect of *Arrabidaea Chica* Verlot on Posttraumatic Neuropathic Pain in Rats

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1. Abstract

The use of medicinal plants is a part of human evolution and plays an important role in the treatment of numerous diseases. Neuropathic pain is caused by an injury or disease of the somatosensory nervous system, which affects about 8% of the world population, and its management is considered a great challenge. In the search for new therapies, *Arrabidaea chica* (Humb. & Bonpl) Verlot, (*A. chica*), popularly known as carajirú and pariri, whose anti-inflammatory properties are scientifically proven and without evidence of neuropathic pain, appears in this scenario. The objective of this study was to evaluate the efficacy of fractions of the ethanolic extract of *Arrabidaea chica* in an experimental model of neuropathic pain induced by compression of the main trunk of the ciatic nerve in Wistar rats. After obtaining the extract by maceration with ethanol, fractionation was carried out to obtain fractions: hexane, chloroform, ethyl acetate and butanol. In vivo studies were performed using the von Frey, Rotarod and Weight bearing tests. The animals were treated for 15 days with the fractions of *Arrabidaea chica* at the dose 1 mg/kg/day. Gabapentin (1 mg/kg v.o) was used as a positive control. The pharmacological study significantly attenuated the behavioral manifestations of neuropathic pain in the animals treated with the fractions of the ethanolic extract of *Arrabidaea* the dose 1 mg/Kg v.o, compared to the saline group (0.1 ml/kg), confirming the antinociceptive action and antioxidants of the plant. In conclusion, the results of this study suggest that the fractions of *Arrabidaea chica* present therapeutic potential for the treatment of neuropathic pain and/or adjuvant in the conventional treatment of the same.

2. Introduction

Throughout the evolutionary historical process of man, medicinal plants have always played an important role in

the search for relief of their ills, being considered as the first therapeutic resources used from popular experiences disseminated by different ethnicgroups around the world [1]. The World Health Organization estimates that 80% of the world's population makes use of medicinal plants as a therapeutic resource [2]. About 30% to 60% of the available therapeutic drugs are derived from natural sources, mainly from plants and microorganisms [3-5].

Brazilian biodiversity is among the largest in the world comprising more than 45,000 species of higher plants. Due to this biodiversity, many of these plants are used in the form of infuso or decocto for the control of different types of diseases, many of which have scientific studies proving these actions [6,7].

Among these species, we *highlight Arrabidaea chica* (Humb. & Bonpl) Verlot (*A. chica*) of the family Bignoniaceae, popularly known by several names in the northern and northeastern regions of Brazil, but especially as carajirú and pariri and widely used in traditional medicine as a medicinal plant to treat inflammatory processes, abdominal pain, gastrointestinal disorders, enterocolite, leukemias, anemias [8], infections fungal diseases and herpes, as well as used in the cleaning of chronic wounds [9].

The species *A. chica* composes the National List of Medicinal Plants of Interest to the Unified Health System (RENISUS) published by the Ministry of Health in 2009 with the purpose of guiding studies and research that can support the elaboration of a list of medicinal and herbal plants to be made available for the use of the population, safely and effectively for the treatment of a given disease [10].

Pharmacological and biological studies *of A. chica* prove therapeutic properties with hypotensive, anti-inflammatory, diuretic, healing, antimicrobial, antitumor, antioxidant and antiprotozoa actions [11-16], but we did not find published data of antinociceptive action of the plant species in the prophylaxis and treatment of neuropathic pain in an animal model.

Neuropathic pain is a clinical category caused by injury or disease of the somatosensory nervous system and includes several chronic conditions that together reach up to 8% of the world population [17]. It is a debilitating pathology that affects the quality of life, physical and mental health of patients and represents a great challenge in its clinical management [17,18].

Due to the complexity of the mechanisms involved in neuropathic pain, we do not have in the market ideal drugs, with specific drugs that present a peripheral and central action with minimal adverse effects [19]. Considering also the great socioeconomic impact resulting from neuropathic pain, it is essential to develop new safe antinociceptives with reduced side effects, for the use of effective therapies, with fewer adverse effects and that provide greater treatment adhering by patients.

In this perspective, the plant *species A. chica* Verlot, appears as a promising source in the research of active substances with potential that can ensure an effective and safe therapy for the treatment of neuropathic pain. Thus, the objective of this study was to evaluate the efficacy of antinociceptive activity of *A. chica* Verlot fractions in an experimental model of neuropathic pain in rats.

3. Materials and Methods

The study was carried out at the Experimental Laboratory of Pain Study (LEED), after the approval of the Animal Ethics Committee (CEUA) of the Federal University of Maranhão (UFMA) under protocol CEUA-UFMA no. 2311006040/2013-04.

3.1 Plant species

The leaves of *A. chica* (Humb. & Bonpl.) Verlot (350 g) were collected in the Medicinal Garden "Profª Berta Lange de Morretes" of the Attic Herbarium Seabra at the Dom Delgado Campus of the Federal University of Maranhão (UFMA) in the municipality of São Luís (Latitude: 02° 31' 47" S Longitude: 44° 18' 10" W and Altitude: 24 m) in October 2015. The species was identified in the Herbarium "Ático Seabra" - UFMA and exsicata of the material (No. 1067) is deposited in this Herbarium.

3.2 Fractionation of the ethanolic extract of the leaves of *Arrabidaea chica*

Part of the ethanolic extract *of A. chica* (9.08 g) was dissolved in 100 mL of the mixture methanol/water (70:30, v/v) by stirring and submitted to liquid-liquid partitionusing hexane, chloroform, ethyl acetate and n-butanol. The extractive solutions were filtered (Na_2SO_4 anhydrous) and concentrated in rotary evaporator under vacuum, obtaining the fractions of hex (FH), chloroform (FC), ethyl acetate (FAE) and butanolic (FBU).

3.3 Animals

In this study, 40 Wistar rats, *Rattus norvegicus*, adults, males and females with weight variation between 150 and 300 g provided by the Central Biotery of UFMA were used. The

animals were kept in the Sectorial Bioterium of the Research and Graduate Building CCBS/UFMA, under controlled light conditions (light/dark cycle of 12 hours) at a temperature of 22 ± 2°C and air humidity 40 to 60%, with commercial feed of the brand Labina® and water *ad libitum*.

3.4 Characterization of the type of study and selection of the sample

This study was characterized as an experimental preclinical trial, with random distribution of animal groups. To perform the experimental procedures, the ethical standards of the *International Association for Study of Pain* (IASP) were commenced, which regulate experiments carried out on animals COMMITEE FOR RESEARCH AND ETHICAL ISSUES OF THE IASP, 1983).

3.5 Experimental design

The animals were divided into three experimental groups thus distributed:

1) Control (n=05): animals that were not submitted to any type of surgical intervention.

2) SHAM (n=05): animals in which tissue incision was made until visualization of the sciatic nerve, but the nerve was not compressed.

3) Surgical with compression (n=30): animals in which the sciatic nerve was isolated and compressed into the common trunk. This group was divided into six subgroups each with five animals, named: FH, HR, FAE, FBU, saline group and gabapentin positive control. The subgroups FH, HR, FAE and FBU were treated orally with the different fractions of the extract at the dose 1 mg/Kg, the positive control group received gabapentin (1 mg/Kg v.o) and the Saline Group NaCl 0.9% (0.1 ml/Kg). The animals were treated on the first day (D1) after induction until the fifteenth day (D15). Then the animals were euthanized for blood collection, for biochemical study.

3.6 Experimental model of sciatalgia

The animals were anesthetized with intraperitoneal injection of ketamine hydrochloride 2.5% (90 mg/kg) and xylazine hydrochloride 1.75% (10 mg/kg). After trichotomy, at the site of the procedure, an incision was made parallel to the fibers of the femoral biceps of the right thigh of the animal, thus exposing the sciatic nerve. Following the model described by [20] and modified by our study group, which performed compression in the common trunk of the right paw sciatica with an average force of 0.44 Kgf, through a device developed in our laboratory, with the purpose of inducing neuropathic pain in the path of the sciatic nerve (Patent - BR 10 2017 000325 6, deposited on: 06/01/2017), then the suture was done by planes. The compression force was determined by the researcher's perception of the reflex movement of the injured paw as the compression was performed.

Finishing this procedure, the incision site was sutured with non-absorbable nylon thread and disinfected with rifamycin solution. The animals belonging to the SHAM group were submitted to the anesthetic procedure and sciatic nerve isolation, but did not receive any compression in this nerve. The control group was not submitted to any surgical intervention.

3.7 Forced ambulation - Rotarod test

The animals were placed on the rotarod (model IITC Life Science, California, USA) at a speed of 16 rpm for a period of time of 300 seconds. The use of the affected limb was evaluated by forced ambulation. The use of the paw was graduated on a numerical scale ranging from 5 to 1, in which: 5=normal use of the limb; 4=mild claudication; 3=severe claudication; 2=intermittent disuse of the affected paw; 1=complete disuse of the affected paw [21].

3.8 Mechanical Allodinia - Von Frey Test

Mechanical allodinia was performed with a digital allotgesimeter (Insight model, São Paulo, Brazil), which consists of a pressure transducer connected to a digital power counter expressed in grams (g). The contact of the pressure transducer with the paw of the animals was made by means of a disposable polypropylene tip with 0.5 mm diameter adapted to the apparatus [21,22].

To adapt with the environment, the animals were placed in acrylic boxes measuring 12 x 20 x 17 cm, whose floor consists of a mesh network of 5 mm^2, consisting of non-malleable wire of 1 mm thickness, for 15 minutes before the experiment. Mirrors were positioned 25 cm below the experimental boxes to facilitate the visualization of the plantar region of the animals' paws. The experimenter applied, through the mesh of the net, a linearly increasing pressure in the center of the plantar region of the rat's paw until the animal produces a response characterized as shaken ("*flinch*") of the stimulated paw. The stimuli were repeated up to six times, in the ipsilateral and contralateral paws, until the animal presented three similar measures of response "*flinch*" after the removal of the paw [21,22].

The nociceptive paw removal threshold (LNRP) was

defined as the force percentage to cause an active suspension in the affected ipsilateral paw and was determined as follows:

$$\text{LNRP (\%)} = \frac{\text{LNRPA}}{\text{LNRPA + LNRPC}} \text{X100}$$

Where:

LNRP is the nociceptive threshold of paw removal;

LNRPA is nociceptive threshold of removal of the affected paw;

LNRPC nociceptive threshold of removal of the contralateral paw.

3.9 Infunctional capacity - Weight bearing test

The animals are placed in an angled glass chamber and positioned, so that each hind paw rests on different platforms. The weight exercised on each hind paw (measured in grams) was evaluated in a period of five seconds. The final measurement of the weight distribution was given by an average of three measurements. Changes in weight distribution in the hind legs were calculated as follows:

$$\text{Weight distribution (\%)} = \frac{\text{PPA}}{\text{PPA + PPC}} \text{X100}$$

Where:

PPA is the weight of the affected paw;

PPC the weight of the contralateral paw.

4. Statistical Analysis

The comparison of the means of different experimental groups was performed with student's t-test or univariate variance analysis (One-way ANOVA), followed by the Newman Keuls test. In the evaluation of two sources of variability, bivariate variance analysis (TWO-way - ANOVA) was used. The value of $p<0.05$ will be considered as indicative of significance and the data obtained were analyzed using the software "graph pad Instal® (Graph Pad software, San Diego, CA).

5. Results

5.1 Effect of *Arrabidaea chica fractions* on neuropathic pain

Analysis of mechanical allodinia in animals treated with EEAC fractions after induction of DN - Von Frey test: Figure 1 shows that on the first day after induction of DN, there was an increase in the nociceptive threshold of the ipsilateral paw of the animals, indicating mechanical allodinia among the studied groups: SALINA (16.13%); SHAM (6.91%), GABAPENTIN (16.13%) and fractions: FH (15.42%), HR (7.91%), FAE (31.28%) and FB (15.42%) when compared to the CONTROL group. The animals treated with CF and FAE showed significant improvement in mechanical allodinia, from the first (D1) to the fifteenth day (D15) of the treatment. Hr in D5 reduced the nociceptive threshold by

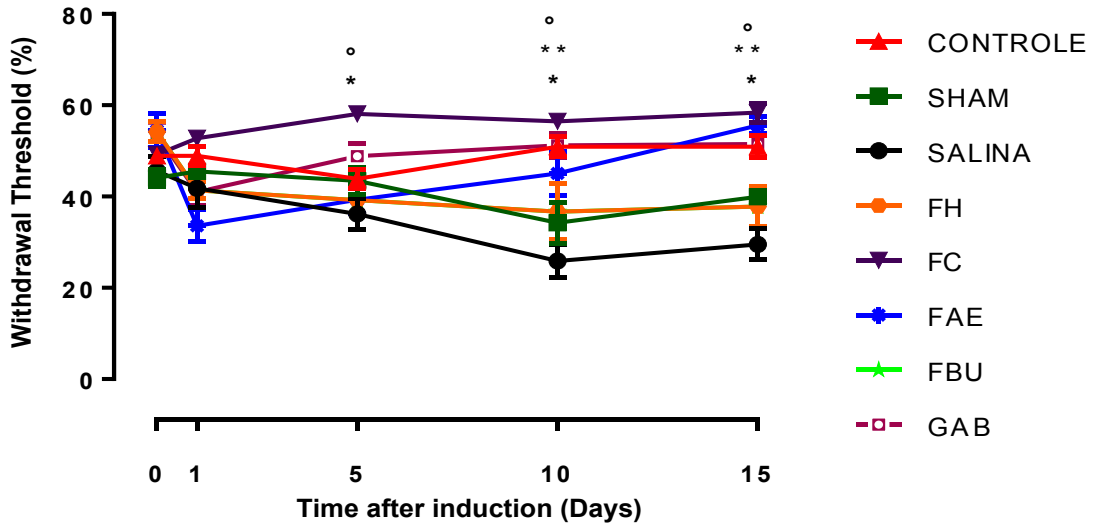

Figure 1: Effect of oral administration of the Hexfraction (FH), Chloroform Fraction (CF), EthylAcetate Fraction (FAE) and Butanolic Fraction (FBU) (1 mg/kg, v.o.), obtained from the EthanolExtract of *A. chica*, and gabapentin (GAB, 1 mg/kg) in mechanical allodinia (Von Frey) in an experimental model of neuropathic pain (DN) in rats. ANOVA – Newman Keuls ($p<0.05$). *Difference of the group treated with HR in relation to the SALINA group (D5 to D15). **Difference of the FAE group in relation to the SALINA group (D10 to D15). ºDifference of the GAB group (1 mg/Kg, v.o.), from D5 to D15 in relation to the SALINA group.

37.71%, the nociceptive threshold (p= 0.002), d10 reduced by 45.88% (p<0.0001) and in D15 by 49.53% (p<0.0001). The FAE reduced the nociceptive threshold by 42.40% in D10 (p=0.0018) and 46.96% in D15 (p<0.0001), when compared to the SALINA group.

It should be emphasized that HR and FAE presented intensity of effect similar to gabapentin, which showed a decrease in allodinia on the tenth and fifteenth day after induction of 50.55% and 57.23%, respectively.

Analysis of the locomotor activity of animals treated with EEAC fractions after induction of the DN–Rotarod Test: Figure 2 shows gait impairment on the first day after ND induction, where we observe a reduction in gait score in groups treated with eeac fractions (FH, HR, FAE and FBU), GABAPENTIN and SALINA that presented score 3, which indicates severe claudication (p<0.0001) and sham group, SHAM score 4, indicating mild claudication (p=0.0049), when compared to the CONTROL group (score 5 = normal). The animals treated with CF and FAE showed improvements in gait score from fifth to fifteenth of 26% and 20% respectively (score = 4, p = 0.0314) when compared to the SALINA group (score = 3). In D15, the animals treated with FH showed improvement of 33.33% in gait (score = 4), as well as those treated with FAE that showed the same behavior of positive control animals treated with gabapentin of 26.6% (score = 3.8) when compared to the SALINA group (score = 3).

Evaluation of weight distribution in hind legs after induction of neuropathic pain – weigths-bearing test in animals treated with EEAC fractions: For the behavioral weight discharge test, the difference between the values of weight discharge in the hind legs of the animals was considered, that is, the difference between the ipsilateral paw and the contralateral paw of the lesion, according to equation 2 (item 4.7.4). The values are expressed in (%) and the higher values in the contralateral paws *indicate stake-sustaining defict* in the ipsilateral paw indicating hyperalgesia in the injured paw. Figure 3 shows that on the first day after induction of ND, there was a reduction in the nociceptive threshold in the ipsilateral paw between the groups: SALINA (51.31%), SHAM (14.79%), HR (22.45%), FBU (17.87%), FAE (58.03), FH (43.57%) and the GABAPENTIN control group (65.06%), when compared to the CONTROL group. The animals treated with CF, FBU and FAE showed significant improvement from D5 to D15, when compared to the SALINA group, in D15 hr induced an increase of 73.66%, FBU increased the nociceptive threshold by 43.15%.(HR in D5 with p = 0.0146, D10 *with* p=0.0239 and D15 p <0.0001, The FBU in D5 *with* p <0.0001, D10 *with* p <0.0001 and D15 with p=0.013), in D15 GABAPENTin (p=0.0003) and FAE (p=0.0210) showed an increase of 32.64% and 41.39%, respectively when compared to the SALINA group.

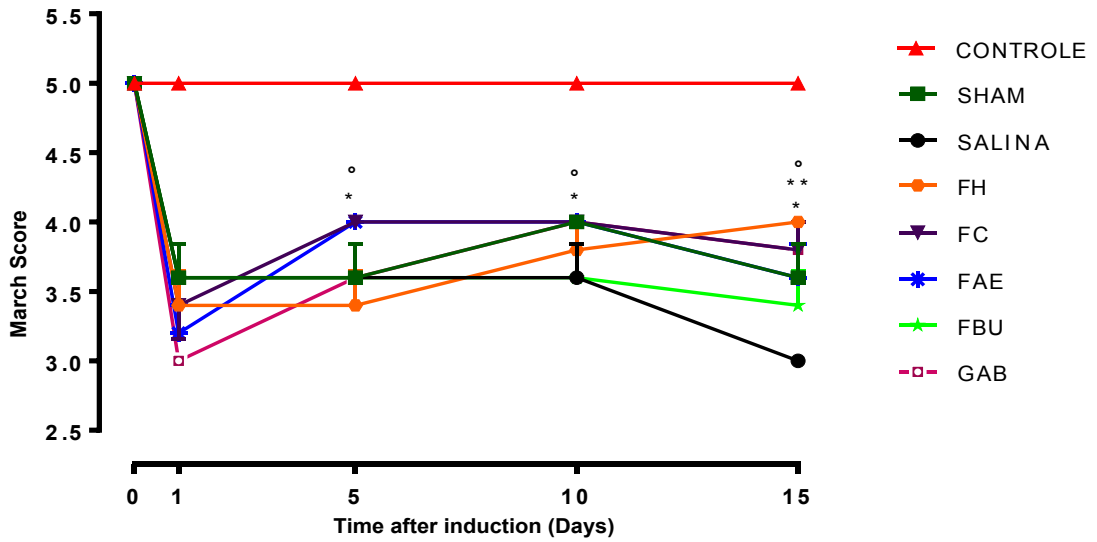

Figure 2: Effect of oral administration of the Hexfraction (FH), Chloroform Fraction (FC), EthylAcetate Fraction (FAE) and Butanolic Fraction (FBU) (1 mg/kg, v.o.), obtained from theEthanol extract of *A. chica* and gabapentin (GAB, 1 mg/kg) in gait (Rota rod), in an experimental model of neuropathic pain in rats. ANOVA – Newman Keuls (p< 0.05). *Differences in the groups treated with CF and FAE in relation to the SALINA group (D5 to D15). **Difference of the FH group in relation to the SALINA group (in D15). the gab group (1 mg/kg, v.o.) (D5 to D15) indicatesdifference in relation to the SALINA group.

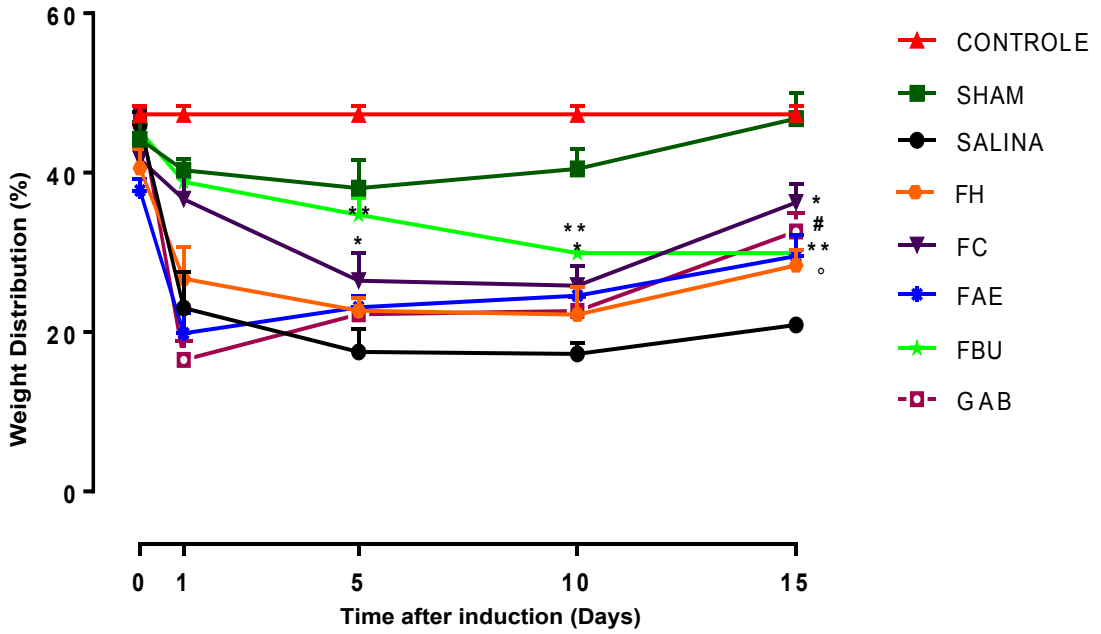

Figure 3: Effect of oral administration of the Hexfraction (FH), Chloroform Fraction (FC), EthylAcetate Fraction (FAE) and Butanolic Fraction (FBU) (1 mg/kg, v.o.), obtained from the ethanol extract of *A. chica*, and gabapentin (GAB, 1 mg/kg) in the distribution of weight in the hind legs in an experimental model of neuropathic pain in rats. ANOVA – Newman Keuls (p<0.05). *Difference of the group treated with HR in relation to the SALINA group (D5 to D15). **Difference of the FBU group in relation to the SALINA group (D5 to D15). ºDifference of the GAB group (1 mg/Kg, v.o.), in D15 in relation to the SALINA group. #Difference of the FAEgroup in relation to the SALINA group.

6. Discussion

Neuropathic pain is a clinical category caused by injury or disease of the somatosensory nervous system and includes several chronic conditions that together affect up to 8% of the world population (GILRON; BARON; JENSEN, 2015). It is a debilitating pathology that affects the quality of life, physical and mental health of patients and represents a great challenge in its clinical management (SCHMADER, 2002; GILRON; BARON; JENSEN, 2015).

Due to the complexity of the mechanisms involved in neuropathic pain, we do not have in the market ideal drugs, with specific drugs that present a peripheral and central action with minimal adverse effects (BAHAREH; HOSSEIN, 2012).

In this study, the efficacy of the therapeutic potential of the fractions of the ethanol extract *of Arrabidaea chica* (EEAC) was evaluated in an experimental model of neuropathic pain (DN).

The fractions obtained from the EEAC were evaluated in the von Frey test. In this test it was observed that the injured paws of the animals of all groups presented a significant increase in hyperalgesia, compared to the healthy paws. The treatment of animals with CF and FAE (1 mg/kg) reduced mechanical allodinia in the ipsilateral paw of the animals. In addition, the fractions (HR and FAE) presented the intensity of effect similar to gabapentin (1 mg/kg), a drug used as a positive control in the experiments and also presented analgesic action when compared to the saline group (Figure 1).

Gabapentin is a reference drug used to control neuropathic pain that decreases inflammatory markers such as COX-2, PGE-2, NO, IL-1b and MMP2. Its antinociceptive effect seems to be related to the performance in neuronal calcium channels and decreased glutaminergic transmission [23-25].

One of the factors that play an important role in the induction of neuropathic pain is the reduction of levels or function of gamma amino butyric acid (GABA), a major inhibitory neurotransmitter of the central nervous system, after induction of neuropathic pain [26]. Some flavonoids extracted from plants are known as partial GABA agonists and modulators of the action of benzodiazepines [27]. This is relevant forthe results of this study since the eeac fractions such as FH, HR and FAE showed higher concentrations of flavonoids in their composition. Phytochemical approach

studies conducted by (ALVES et al. 2010; Ribeiro et al. 2012), indicate the presence of chemical classes such as: reducing sugars, anthocyanidins, anthocyanins, anthraquiones, steroids, triterpenóides, phenols, flavanonols, flavanols, flavanones, saponins and catéchic tannins, these results corroborate this study.

In addition to probable central mechanisms that may be involved in the antinociceptive action of eeac fractions, it is also possible that this may occur by a peripheral action, as evidenced in another species of the same genus, *Arrabidaea brachypoda*, which presents similarity in relation to major secondary metabolites. *A. brachypoda* showed peripheral antinociceptive effect, in addition to anti-inflammatory activity, by inhibiting the recruitment of leukocytes in a model of peritonitis induced by polysaccharides [28].

For the locomotor activity test, the animals treated with the hemonic, chloroform, ethyl acetate fractions showed significant improvements in the gait score evaluated by rotarod when compared to the saline group (Figure 2). The group treated with gabapentin, at the same dose used for the fractions, had a similar effect to that of the animals treated with these fractions. It is noteworthy that these fractions presented the highest content of total polyphenolics and flavonoids, active substances that should be responsible for the pharmacological effects *of A. chica*.

Another test was the evaluation of hyperalgesia in the injured paw by the weight bearing method, which showed that the animals treated with the following fractions: HR, FH, FAC and FBU showed improvement in the nociceptive threshold, when compared with the saline group. As expected, the group treated with gabapentin presented analgesic action, and this effect was similar to that observed in the groups treated with fractions (Figure 3).

Corroborating the results of the research, thestudy by Zorn et al. [29] suggest that these effects may be related to the anti-inflammatory activity of the EEAC, when it was observed that *the extract of A. chica* inhibited the nuclear transcription factor kappa B, thereby preventing the formation of cytokines and inflammatory enzymes such as iNOS, COX-2, 5-LOX and cytosolic Phospholipase A2 . Pain is closely related to the inflammatory process since inflammatory mediators released with tissue injury modify the transmission and excitability of nociceptors in such a way that previously mild or ineffective stimuli become painful [30,31].

Recently, it has been reported that pro-inflammatory cytokines, such as interleukin-1b (IL-1b) and nitric oxide (NO) produced by immune cells, astroglia and microglia, in the spinal cord play an important role in the pathogenesis of neuropathic pain [32]. These factors initiate a cascade of neuroinflammation and related events that can remain and worsen the original lesion, causing pain and chronicity [33]. In addition, inflammation induces cyclooxygenase-2 (COX-2), which in turn results in the production of prostaglandins (PGE) [34]. PGE2 is a pain-inducing factor, capable of sensitizing primary sensory neurons, generating central sensitization and facilitating the release of pain-related neuropeptides [35].

Studies conducted by Michel and collaborators in 2015 showed the action of *ethanol extract of A. chica* as an anti-inflammatory agent and attributed this activity to flavonoids, luteolin and canferol present in the extract. [36] studied the effects of aqueous extract *of A. chica on venom-induced* edema *of bothrops atrox and Crotalus durissus ruruima snakes in* oral, intraperitoneal and subcutaneous albino mice. The results indicated that the extract contains chemicals with anti-inflammatory activity.

This study identified compounds such as flavonoids, anthocyanidins, and triterpenes in the active fractions of EECA and which are probably the active substances involved in the antinociceptive action of the extract and fractions of *A. chica*.

In addition to the mechanisms of genesis mentioned above, there is evidence to prove that antioxidant agents play a determining role in neuropathic pain. Oxidative stress results from an imbalance between the generation of oxidizing compounds and the performance of antioxidant defense systems and being involved in the pathogenesis of neuropathic pain [37]. There are enzymatic and non-enzymatic antioxidant substances that act on cell protection. Among the enzymatics can be mentioned superoxide dismutase, catalase and glutathione peroxidase. Flavonoids were identified in the FH and FAE fractions, flavone (carajuflavone, rutin, apigenin and myricetin), anthocyanidins, which are antioxidant substances, were identified.

Inflammatory cytokines are involved in central sensitization induced by nerve injury and/or inflammation and are related to the appearance of hyperalgesia and allodinia. Inflammatory responses in the somatosensory nervous system play key roles in the evolution and persistence in pathological pain. These cytokines are present in the spinal cord, dorsal root ganglia and nerve lesions, are associated with pain and with the generation of abnormal spontaneous activity of nerve fibers or dorsal root ganglia of injured or inflamed neurons [38,39].

In the course of the inflammatory process vasodilation occurs increasing blood flow at the site of injury. Microvascular permeability increases, causing the loss of plasma proteins and fluid to the tissue. At the same time, pro-inflammatory cytokines such as Interleukin 1 β (IL-1β), interleukin 6 (IL6) and Tumor Necrosis Factor (TNF-α) are released by macrophages, activating the regulation of inflammatory reactions. There is evidence that pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) are involved in the process of sensitization of neuropathic pain [40-42].

7. Conclusion

The results obtained in this study show that the fractions of the ethanol extract of *Arrabidaea chica* (EEAC) (1 mg/Kg) present antinociceptive activity in neuropathic pain induced by compression of the sciatic nerve in rats, when administered orally, during 15 days of treatment.

In view of the above, the results prove the antinociceptive action of the EEAC fractions in neuropathic pain, however, other pharmacological investigations are necessary to suggest the mechanism(s) of antinociceptive action and further molecular and cellular investigations are necessary to demonstrate the possible central or peripheral effects in this debilitating chronic condition.

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