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Evaluation of the Anti-Inflammatory Potential of Extracts Methanolics from Catingueira (*Cenostigma Bracteosum*) and Canafistula (*Senna Trachypus*)

Avaliação do Potencial Anti-Inflamatório dos Extratos Metanólicos da Catingueira (*Cenostigma Bracteosum*) e da Canafístula (*Senna Trachypus*)

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ABSTRACT

The use of medicinal plants are ancient practices used by the population to prevent or treat various types of diseases. In the Brazilian Northeast, the use of medicinal plants for the treatment of diseases is widespread with plants easily accessible by the local population and many of these plants have not yet had their effectiveness scientifically proven. Taking into account that Catingueira (*Cenostigma bracteosum*) and Canafístula (*Senna trachypus*) are species used by the population and that there is little research about their therapeutic potential, the objective of this work was to evaluate the anti-inflammatory activity of these species. For this experiment, 24 adult Wistar rats of both sexes (180-250g) were used, divided into six groups with 4 (four) animals each, one group for negative control (animals with carrageenan), another for positive control (with dexamethasone), two groups with concentrations of 1% and 10% for formulations with catingueira and canafístula extracts. The gel formulations were topically applied to the right hind paws shortly after the carrageenan injection. After the last measurement of edema, the animals were euthanized for collection and fixation of the hind paws in formalin and preparation of histological slides. It was possible to observe that the gels of the two species studied were effective in reducing the paw edema induced by carrageenan. In the histological evaluation, it was also possible to observe a decrease in neutrophils in the groups treated with catingueira. Thus, it is suggested that the studied species have anti-inflammatory potential.

Keywords: Anti-inflammatory; Fabaceae, Secondary Metabolites;

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RESUMO

O uso de plantas medicinais são práticas milenares utilizadas pela população para prevenir ou tratar diversos tipos de doenças. No Nordeste brasileiro o uso de plantas medicinais para o tratamento de doenças é bastante difundido sendo plantas de fácil acesso pela população local e muitas destas plantas ainda não tiveram sua eficácia comprovada cientificamente. Levando em consideração que Catingueira (Cenostigma bracteosum) e Canafístula (Senna trachypus) são espécies utilizadas pela população e que há poucas pesquisas sobre seu potencial terapêutico, o objetivo deste trabalho foi avaliar a atividade anti-inflamatória destas espécies. Para este experimento foram utilizados 24 ratos Wistar adultos de ambos os sexos (180-250g), divididos em seis grupos com 4 (quatro) animais cada, sendo um grupo para controle negativo (animais com carragenina), outro para controle positivo (com dexametasona). , dois grupos com concentrações de 1% e 10% para formulações com extratos de catingueira e canafístula. As formulações de gel foram aplicadas topicamente nas patas traseiras direitas logo após a injeção de carragenina. Após a última mensuração do edema, os animais foram eutanasiados para coleta e fixação das patas traseiras em formol e confecção de lâminas histológicas. Foi possível observar que os géis das duas espécies estudadas foram eficazes na redução do edema de pata induzido pela carragenina. Na avaliação histológica também foi possível observar diminuição de neutrófilos nos grupos tratados com catingueira. Assim, sugere-se que as espécies estudadas possuam potencial anti-inflamatório.

Palavras-chave: Anti-inflamatório; Fabaceae, Metabólitos Secundários;

INTRODUCTION

A study carried out by the World Health Organization (WHO) evaluated the use of herbal medicines by the world population, with around 80% of the population in developing countries using therapeutic practices transmitted through generations using plants to cure and prevent diseases (OLIVEIRA *et al.*, 2014). In Brazil, this total exceeds 82% of the population that seeks herbal remedies to treat diseases (FÉLIX-SILVA et al., 2012).

Brazil is considered one of the countries with the greatest biodiversity on the planet, this is because the country has around 20% of the total number of species in the world (ALBUQUERQUE *et al.*, 2007; MACIEL *et al.*, 2002), which is extreme cultural importance, as this is considered a large unexplored chemical, biological and genetic repository of technologies with possible scientific and technological applications in several areas, including the pharmaceutical sector (FERRO, 2006).

Among the biomes present in the national territory that make up Brazilian biodiversity, there is the Caatinga, an exclusively Brazilian biome, presenting vegetation considered one of the most threatened on the planet, despite this, this exclusivity was not enough to direct many botanical studies in this area (BRAZIL, 2002). The plants used by

the population in local therapeutics are of constant interest to ethnobotany and ethnopharmacology, through knowledge about their use and application (SHELLEY, 2009; ALBUQUERQUE, 2010).

In the Brazilian Northeast, the use of medicinal plants to treat diseases is quite widespread, with plants easily accessible by the local population (MARREIROS *et al*., 2015). Studies have investigated which medicinal plants and their respective therapeutic purposes are traditionally used by the population of the Caatinga, even with different objectives, it is possible to perceive a growing scientific knowledge about the use of medicinal plants in this Biome (SILVA *et al*., 2015; BARBOSA *et al*. , 2020; LIMA, ARAÚJO and BRITO, 2020; NOVAES and NOVAES, 2021). Among the plant families reported with medicinal potential, the one with the greatest number of species was the Fabaceae family (SÁ-FILHO, 2022), this botanical family constitutes one of the botanical families of greatest economic and medicinal importance (GOMES *et al*., 2008). The approach of popular medicine as an important means for developing new drugs is mentioned in studies with rural communities in the Caatinga (COSTA, 2021), in addition, another study emphasizes the influence of Fabaceae species in northeastern communities, and consequently, in therapeutic use (LOIOLA et al., 2010).

The main therapeutic activities described in research involving plant species from the Fabaceae family report mainly anti-inflammatory, antimicrobial, anti-flu, antioxidant and sedative effects, contributing to the treatment of various illnesses that affect populations (SILVA *et al.*, 2015; SILVA, MIRANDA AND CONCEIÇÃO, 2010; AGRA *et al.*, 2007). In this sense, the objective of this study was to evaluate the anti-inflammatory potential of methanolic extracts from catingueira (*Cenostigma bracteosum*) and canafístula (*Senna trachypus*) leaves belonging to the Fabaceae family.

METHODS

OBTAINING BOTANICAL EXTRACTS FROM "CATINGUEIRA" (*Cenostigma bracteosum*) AND "CANAFÍSTULA" (*Senna trachypus*)

The plants used in this study were collected in the rural area of Mossoró/RN (5°27'55.1"S 37°19'34.2"W). Voucher specimens were prepared and deposited in the "Dárdano de Andrade Lima" herbarium belonging to the Federal Rural University of the Semi-Arid (UFERSA) and identified by the curator of the herbarium. For the production of extracts, leaves of the catingueira (*Cenostigma bracteosum*) and canafístula (*Senna*

trachypus) species were collected, separated, cataloged, and labeled in plastic bags for processing in the laboratory.

In the laboratory, the leaves of both species, properly stored, underwent the drying process in an oven at 35°C until reaching a constant weight (approximately 72 hours). After the drying process, the leaves were ground in a Willey SL-31 knife mill (reduced to small particles) in the Wood Technology laboratory at the Federal Rural University of the Semi-Arid (UFERSA).

With the leaves reduced to powder, it was possible to carry out the extraction process through maceration, using methanol (CH_3OH) as a solvent. The solid part of the material was weighed and subjected to maceration for 7 days (1:10, w/v). Subsequently, the solutions were filtered and taken to the rotary evaporator (QUIMIS® Microprocessed - Q344M) for complete solvent removal. Finally, the extracts were placed in Petri dishes covered with perforated plastic film for evaporation of any remaining solvent residues. After 24 hours, the extracts were transferred to amber glass bottles and stored in a dry place at room temperature and away from light.

FORMULATION OF GEL WITH EXTRACTS

The gel used in this study consisted of Hydroxyethyl cellulose (10%), Glycerin (10%), Nipagin/Nipazol (0.15%/0.10%) in propylene glycol, and Distilled Water. The crude extracts were solubilized in distilled water and glycerin, and then agitation was maintained to ensure the incorporation of the gels. In the end, gels were obtained for each species in two different concentrations: 1% and 10%.

EVALUATION OF ANTI-INFLAMMATORY POTENTIAL

The project under protocol 014/21 was approved by the Ethics Committee on Animal Research of the State University of Rio Grande do Norte and carried out by trained professionals following animal care procedures to minimize animal suffering. The methodology used in this study for in vivo experimentation was adapted from PINHEIRO (2010), PAIVA (2019), and LOPES (2017).

Twenty-four Wistar rats, adults of both sexes (180-250g), from the Biotery of the State University of Rio Grande do Norte (UERN) were used. The animals were housed during the experiment in polycarbonate boxes lined with bedding and remained in the animal facility with a 12-hour light/dark cycle, controlled temperature (25-28°C),

balanced diet, and ad libitum water. Furthermore, the experiments caused little or no discomfort or stress to the animals, according to the definitions of CONCEA for the degree of invasiveness (GI 1), as the induced paw edema occurred subcutaneously, as described later.

ANTI-INFLAMMATORY ACTIVITY

The evaluation of the anti-inflammatory activity of the extracts was performed according to the methodology described by Winter et al., (1962) with modifications. The measurement of the variation in the thickness of the animals paws was carried out using a caliper, and the method with this instrument had been validated by GUZZO (2007). The caliper was placed in the central portion, between the dorsal and ventral surfaces, of each hind paw (right and left), without applying pressure, before and every 1 hour after the different treatments for 4 hours.

After the control measurement, each right hind paw of the animals received subcutaneous administration of 20 µl of 0.1% Carrageenan solution in the subplantar region, using an insulin syringe (needle 12.7 mm x 0.33). The left hind paws received only the introduction and withdrawal of the needle (sham - control). Carrageenan is a drug that has been used for years, constituting a polysaccharide capable of generating tissue inflammatory reaction in rat paws. Tissue damage can be attributed to the intense inflammatory process produced by carrageenan. The inflammatory process induced by this drug has been extensively studied in the model of inflammatory pain in rodent paws (NECAS, 2013).

Rats were divided into 6 (six) groups with 4 (four) animals each, including a negative control group (animals with carrageenan), a positive control group (with topical application of dexamethasone), two groups for formulations with "catingueira" extracts (*Cenostigma bracteosum*) at concentrations of 1% and 10%, respectively, and finally, two groups for formulations with "canafístula" extracts (*Senna trachypus*) at concentrations of 1% and 10%, respectively.

The gel formulations were applied topically, using a spatula, to the right hind paws, immediately after carrageenan injection. Subsequently, the paws were covered with gauze to facilitate contact with the formulations. The animals were kept in individual cages during this phase of the experiment.

HISTOLOGICAL EVALUATION

Four hours after carrageenan application, the last edema measurement was taken, and then the animals were euthanized by decapitation. The hind limbs were sectioned with a scalpel blade and placed in Falcon tubes containing 10% buffered formalin (37% purity formaldehyde diluted in distilled water) and kept at room temperature for at least 12 hours for fixation.

RESULTS AND DISCUSSION

CARRAGEENAN-INDUCED PAW EDEMA

In this study, paw edema in the rats hind limbs was measured using a caliper. Guzoo (2007) had previously validated this instrument, considering it as effective as a plethysmometer for measuring 0.1% carrageenan-induced paw edema. During the experiment, it was observed that the injection of carrageenan was capable of inducing the inflammatory process characterized by edema and inflammatory infiltrate. In the group treated only with carrageenan, it was observed that the maximum volume of edema was reached after the third hour of the experiment, corroborating with what was assessed by Carvalho *et al.* (1999), where carrageenan-induced paw edema reaches its maximum volume 3 hours after the intracutaneous administration of the substance.

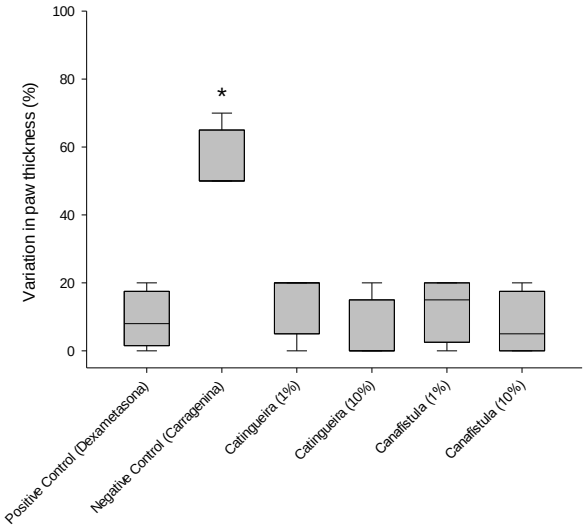
When administered, carrageenan can produce an acute and rapid inflammatory response, increasing thermal and mechanical sensitivity through the release of pro-inflammatory substances such as bradykinin, histamine, tachykinin, complement oxygen, and nitrogen species (MORRIS, 2013). The development of edema in the rat's hind paw after carrageenan injection is the result of the action of various inflammatory mediators that act sequentially to produce an inflammatory response (NECAS, 2013).

It was observed that the topical administration of gel formulations containing catingueira at 1% and 10% and canafístula at 1% and 10% significantly reduced (Figure 1) paw edema ($p \leq 0.05$) 3 hours after carrageenan administration (Table 1). Thus, there is a suggestion of anti-inflammatory activity for these formulations, indicating their potential to control edema similarly to dexamethasone, a classic steroid medication with anti-inflammatory action.

In a study conducted by Santos *et al.* (2011), the antinociceptive and anti-inflammatory effects of the ethanolic extract from the inner bark of catingueira were evaluated. The authors concluded that the extracts significantly reduced nociceptive and

inflammatory responses induced by different agents, including carrageenan. A single oral treatment with the ethanolic extract at a dose of 400 mg/kg reduced carrageenan-induced edema similarly to the inhibition caused by the dexamethasone control (2 mg/kg). This result is similar to the findings in the present study, where the gel based on the same species suggests potential anti-inflammatory effects, and the control, dexamethasone, was the same medication used in this research.

Figure 1. Topical anti-inflammatory activity of gel-based formulations containing extract of Catingueira (*Cenostigma bracteosum*) and Canafístula (*Senna trachypus*) at concentrations 1 and 10%, evaluated by the variation in the thickness of the paws measured before and 3 hours after the administration of 0.1% carrageenan in Wistar rats. The values represent the mean ± mean standard deviation. * $p < 0.05$ compared to the carrageenan group (negative control) (ANOVA followed by Holm-Sidak test).



Source: Own authorship

Table 1: Variation in the thickness of the paws after the injection of carrageenan or the introduction of the needle into the paw, followed or not by topical treatment with formulations containing extracts of Catingueira *(Cenostigma bracteosum*) and Canafístula (*Senna trachypus*) in concentrations of 1 and 10%.

Treatment	Average weight of animals (g)	Variation in leg thickness (mm)
Dexamethasone	192.25 ± 2.66	5.86 ± 2.19
Carragenina	144.00 ± 2.34	23.72 ± 2.38
Catingueira 1%	216.75 ± 6.22	7.31 ± 2.44
Catingueira 10%	228.00 ± 5.61	2.47 ± 2.47
Canafistula 1%	225.75 ± 15.41	6.24 ± 2.37
Canafistula 10%	237.50 ± 4.41	3.80 ± 2.35

Source: Own authorship

Moraes *et al.* (2020) demonstrated in their results that the ethyl acetate fraction of an ethanolic extract from the bark of catingueira has a strong in vitro antioxidant effect, as well as in vivo antinociceptive and anti-inflammatory activities. This can be attributed to the fact that the bark is rich in phenolic compounds derived from gallic acid. Considering that the solvent used in the preparation of the extract can influence the extracted compounds (SILVA, 2019), it is possible to observe that both the ethanolic extracts described in the literature and the gel based on the methanolic extract used in this study were able to extract metabolites with potential anti-inflammatory properties. Thus, it is suggested that research using different parts of the species be conducted to confirm its therapeutic action and find a safe and effective dose for consumption to contribute to those who use the species and serve as a starting point for the development of new medications.

França (2021) identified that the methanolic extract of the flower of *S. trachypus* is rich in flavonoids (rutin, kaempferol-3-O-glucorhamnoside, narirutin, and quercetin), justifying its antioxidant power, and suggesting the development of phyto-medications with cytotoxic properties. Quercetin and kaempferol are flavonols widely distributed in the plant kingdom and have a significant anti-inflammatory action, which can be attributed to the inhibition of phospholipase enzymes (KVIETYS and GRANGER, 2012). The ethanolic extract of the leaf also showed a high content of flavonoids (BASBAUM *et al.*, 2010). These findings support the present study, suggesting an anti-inflammatory potential of canafístula. However, research on this species is still scarce, and more experiments testing its efficacy are needed.

HISTOLOGICAL EVALUATION

The application of carrageenan can cause edema, damage blood vessels, potentiate endotoxicity, induce pain, and recruit neutrophils and macrophages to the injured area (MORRIS, 2013). Figure 2 consists of the quantity of neutrophils found per field in the histological sections of the animals' paws. It was possible to observe an intense infiltration of neutrophils in the group treated only with carrageenan (Figure 2). Neutrophils are highly mobile phagocytic cells that constitute the first line of defense in the innate immune system in circulation (SEGAL, 2005).

Figure 2: Number of neutrophils at 400x magnification in 10 fields.

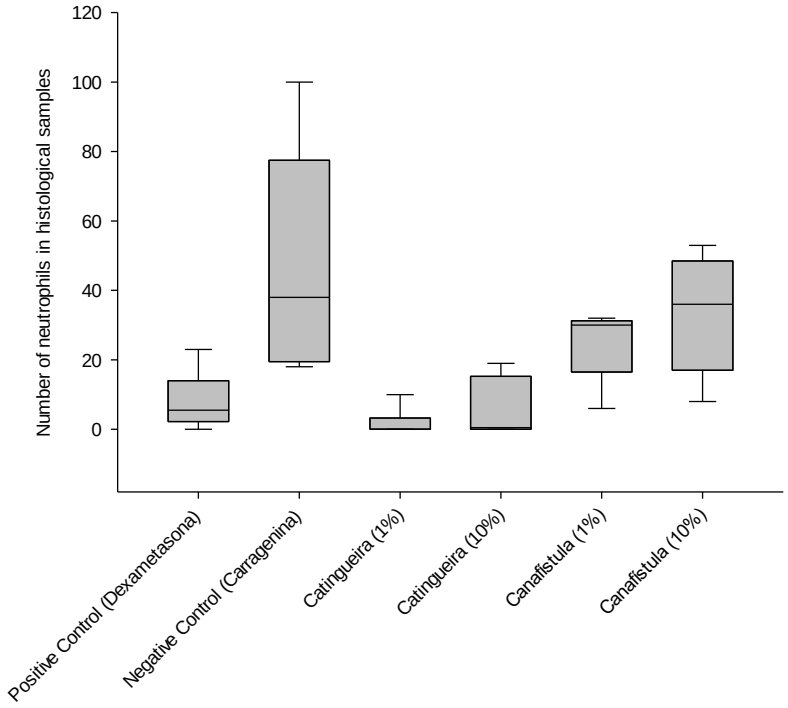


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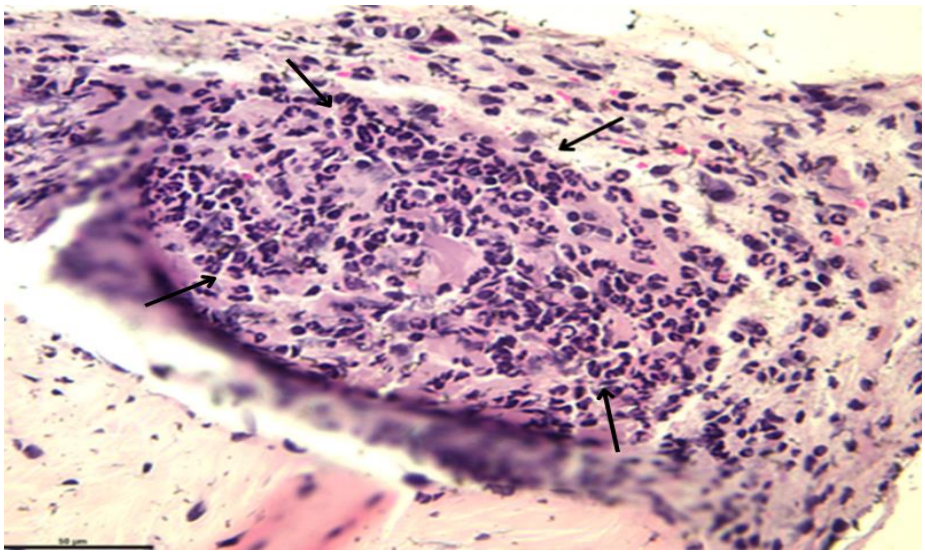
Figure 2: 400x magnification histological cross-section image of the hind leg of the group of Wistar rats that received only carrageenan without any treatment. The arrow shows a cluster of neutrophils.



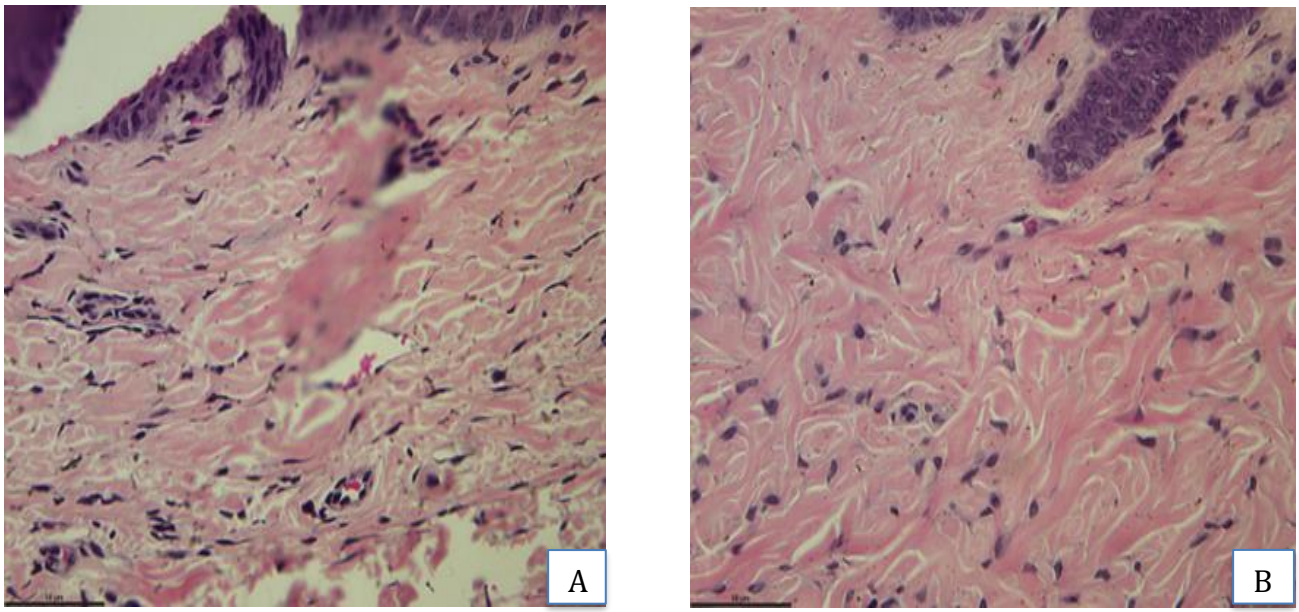
Source: Own authorship

In the group treated with catingueira gels at 1% and 10%, a reduction in neutrophils was observed (Figure 3), with the 10% concentration showing a similar effect to dexamethasone, and the 1% concentration having a lower quantity than the control.

Moraes *et al.* (2020), tested the effect of the ethanolic extract from the bark on hemorrhagic cystitis and observed that it was possible to reduce the accumulation of neutrophils in the tissue. In addition to inhibiting leukocyte infiltration, the dose used tended to reduce edema, hemorrhage, mucosal erosion, and ulceration of the urinary bladder.

Interestingly, the higher dose used did not show a significant improvement in the histology of the urinary bladder tissue. These findings suggest a strong anti-inflammatory potential of the species under study, but further research with different tests and dosages is still needed to identify the correct form of use.

Figure 3: Image of histological sections at 400x magnification of the hind leg of the group of Wistar rats that received application of carrageenan and catingueira gel. A: Received 1% catingueira gel treatment; B: Received 10% catingueira gel treatment.



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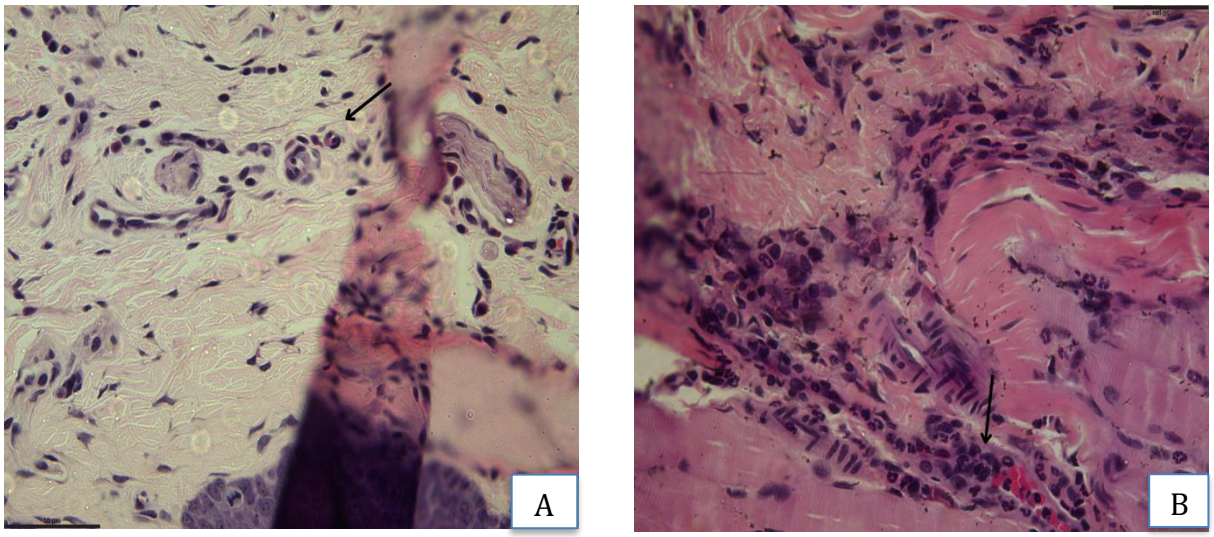
In the groups treated with canafístula, a higher quantity of neutrophils was observed (Figure 4). Considering that the species was able to reduce paw edema, however, in the histological evaluation, a high number of neutrophils was found, suggesting that the plant could activate the granulocyte colony-stimulating factor (G-CSF). G-CSF is a cytokine used in pharmaceutical preparations for the treatment of

neutropenia. Systemic administration of G-CSF is associated with an increase in the neutrophil count in peripheral blood (STEPHANIE *et al*., 2021).

Figure 4: Image of histological sections at 400x magnification of the hind leg of the group of Wistar rats that received application of carrageenan and cannafistula gel. A: Received 1% canafístula gel treatment; B: Received 10% catingueira gel treatment. Arrows indicate neutrophils by the tissue even after treatment.



Source: Own authorship

Neutrophils are terminally formed through the proliferation and differentiation of bone marrow precursor cells during hematopoiesis and, through the stimulation of cytokines, primarily granulocyte colony-stimulating factor (G-CSF), culminate in their formation through a process called myelopoiesis at a rate of 10^{11} per day, reaching up to 10^{12} per day during an infection (MAYADAS *et al.*, 2013).

G-CSF is produced by bone marrow stromal cells, fibroblasts, endothelial cells, monocytes, and macrophages. It mainly acts by promoting the maturation of neutrophils and stimulating their phagocytic and chemotactic activity, as well as being involved in the nuclear segmentation process of mature neutrophils. It can also modulate the inflammatory response by reducing the release of pro-inflammatory cytokines by activated monocytes and macrophages (GOMES, 2008). Additionally, it is widely known as a hematopoietic cytokine that promotes the survival, proliferation, and differentiation of neutrophil lineage cells.

Within the central nervous system, G-CSF has pleiotropic actions. In recent years, the beneficial effects of G-CSF have been demonstrated in rodent models of stroke. For example, G-CSF has shown neuroprotective activity by inhibiting apoptosis and

inflammation in stroke and ischemia models. This occurs because precursor cells respond to G-CSF stimulation, initiating the proliferation and differentiation of precursors into mature granulocytes (KADOTA *et al*., 2020).

There is growing evidence linking G-CSF to neuroinflammation (LI *et al.,* 2015). In a study by Dumbuya et al., 2020, it was demonstrated that treatment with G-CSF in neonatal rats resulted in a faster recovery from inflammation, suggesting a neuroprotective effect. The effects of G-CSF were through the phosphorylation of S6K, thereby increasing cell survival and other cellular processes, decreasing pro-apoptotic mediators, and regulating inflammatory responses in the injured brain.

FINAL CONSIDERATIONS

The gels of the two species studied were effective in inhibiting carrageenan-induced paw edema, as the edema inhibition was similar to the anti-inflammatory used as a standard, dexamethasone. This suggests an anti-inflammatory potential of these species, supporting their popular use.

Through histological evaluation, a decrease in neutrophils was observed in the groups treated with 'catingueira', confirming the anti-inflammatory effect seen in the paw edema test conducted in this study. However, the extract of 'canafístula' showed that there was no decrease in neutrophils as expected. This may have occurred due to the activation of granulocyte colony-stimulating factor (G-CSF).

Considering that the amount of studies on the therapeutic potential of the studied species is still scarce, especially for *Senna trachypus*. The findings in this study contribute to highlighting the potential of the studied species, as they are widely used by the population, even without scientific evidence of their therapeutic action. Their use is based on popular knowledge, as with many other species found in the Brazilian flora. More in-depth research is needed, with different tests at different dosages, to identify the appropriate dose for administration, as well as being conducive to the creation of new drugs and possible patents. In vitro tests are also indicated, considering that handling animals presents difficulties, especially with topical applications.

REFERÊNCIAS

Agra, M. F.; Baracho, G. S.; Nurit, K.; Basílio, I. J. L. D.; Coelho, V. P. M. Medicinal and poisonous diversity of the flora of "Cariri Paraibano", Brazil. **Journal of Ethnopharmacology**, v. 111, n. 2, p. 383–395, 2007.

Albuquerque, U.P. Implications of ethnobotanical studies on bioprospecting strategies of new drugs in semi-arid regions. **The Open Complementary Medicine Journal**, v. 2, p. 21-23, 2010.

Albuquerque, U.P; Oliveira, R.F. Is the use-impact on native caatinga species in Brazil reduced by the high species richness of medicinal plants? **Journal of Ethnopharmacology**, v. 113, p.156–170, 2007.

Aschauer-Wallner, S. *et al.* Granulocyte colony-stimulating factor in traumatic spinal cord injury. **Drug discovery today**, v. 26, n. 7, p. 1642-1655, 2021.

Barbosa, E. U. G., Carvalho, T. K. N., Ferreira, E. C., Santos, S. S., & Lucena, R. F. P. Conhecimento botânico local de agricultores do semiárido do Estado da Paraíba, Nordeste do Brasil. **Polibotánica**, (50), 191-208, 2020.

Basbaum, A. I. *et al.* Cellular and Molecular Mechanisms of Pain. **Cell.**, v. 139, n. 2, p. 267–284, 2010.

BRASIL. Ministério do Meio Ambiente. Biodiversidade da caatinga: áreas e ações prioritárias para a conservação. Brasília: Ministério do Meio Ambiente e Universidade Federal de Pernambuco, 36p, 2002.

Carvalho, J.C.T., Sertié, J.A.A., Barbosa, M.V.J., Patrício, K.C.M., Caputo, L.R.G., Sarti, S.J., Ferreira, L.P., Bastos, J.K. Anti-inflammatory activity of the crude extract from the fruits of *Pterodon emarginatus* Vog. **Journal of Ethnopharmacology** 64, 127-133, 1999.

Costa, A. P. A utilização de plantas medicinais na região nordeste do Brasil: uma revisão. Universidade Federal de Campina Grande, Cuité, PB, Brasil, 2021.

Félix-Silva, J.; Tomaz, I. M.; Silva, M. G.; Santos, K. S. C. R.; Silva-Júnior, A. A.; Carvalho, M. C. R. D.; Soares, L. A. L.; Fernandes-Pedrosa, M. F. Identificação botânica e química de espécies vegetais de uso popular no Rio Grande do Norte, Brasil. **Revista Brasileira de Plantas Medicinais**, v. 14, n. 3, p. 548-555, 2012.

Ferro, D. **Fitoterapia: conceitos clínicos**. Atheneu, 2006.

Franca, Maria Gleiziane Araújo. Estudo de espécies de Senna da Caatinga e do Cerrado: documentação química e farmacológica na busca de novos fármacos. 2021.

Gomes, E. C. S., Barbosa, J., Vilar, F. C. R., Perez, J. O., Vilar, R. C., Freire, J. L. O., Lima, A. N., Dias, T. J. Plantas da Caatinga de uso terapêutico: Levantamento Etnobotânico. **Engenharia Ambiental: Pesquisa e Tecnologia**, 5(2), 74-85, 2008.

Guzzo, L.S., 2007. Avaliação de Atividades Farmacológicas de diferentes Espécies de Lychnophora utilizadas pela população. Dissertação de Mestrado – Programa de Pós Graduação em Ciências Biológicas, Universidade Federal de Ouro Preto, 99p.

Kadota, K. *et al.* Controlled release behavior of curcumin from kappa-carrageenan gels with flexible texture by the addition of metal chlorides. **Food Hydrocolloids**, v. 101, p. 105564, 2020.

Kvietys, P.; Granger, D.N. Role of reactive oxygen and nitrogen species in the vascular responses to inflammation**. Free Radical Biology & Medicine**, v.52, p.556-592, 2012.

Li, L. *et al*. G-CSF attenuates neuroinflammation and stabilizes the blood–brain barrier via the PI3K/Akt/GSK-3β signaling pathway following neonatal hypoxia-ischemia in rats. **Experimental neurology**, v. 272, p. 135-144, 2015.

Lima, S. C. G., Araújo, E. C., Brito, S. F. Ocorrência e caracterização de plantas com propriedades medicinais na caatinga de Arneiroz, Ceará. **Essentia-Revista de Cultura, Ciência e Tecnologia da UVA**, 21(2), 2020.

Loiola, M. I. B., Paterno, G. B. C., Diniz, J. A., Calado, J.F., & Oliveira, A.C. P. Leguminosas e seu potencial de uso em comunidades rurais de São Miguel do Gostoso RN. Revista Caatinga, 23(3), 59-70, 2010.

Lopes, F. M. *et al*. Mimicking Parkinson's disease in a dish: merits and pitfalls of the most commonly used dopaminergic in vitro models. **NeuroMolecular Medicine**, v. 19, p. 241-255, 2017.

Maciel, M. A. M., Pinto, A.C., & Veiga Jr, V.F. Plantas Medicinais, a necessidade de estudos multidisciplinares. **Química Nova**, 25(3), 429-438, 2002.

Marreiros, N. A., Ferreira, E. C., Lucena, C. M., & Lucena, R. F. P. Conhecimento botânico tradicional sobre plantas medicinais no semiárido da Paraíba (Nordeste, Brasil). **Revista Ouricuri**, 5(1), 110-144, 2015.

Mayadas, T. N.; Cullere, X.; Lowell, C. A. The multifaceted functions of neutrophils. **Annual Review of Pathology**, v. 9, p. 181-218, 2013.

Moraes, S. Z. C. *et al*. Antinociceptive and anti-inflammatory effect of *Poincianella pyramidalis* (Tul.) LP Queiroz. **Journal of ethnopharmacology**, v. 254, p. 112563, 2020.

Morris, C. J. Carrageenan-Induced Paw Edema in the Rat and Mouse. In: WINYARD, P. G.; WILLOUGHBY, D. A. **Inflammation protocols**. Totowa, NJ: Humana Press, p. 115-121, 2013.

Necas, J.; Bartosikova, L. Carrageenan: a review. **Vet. Med., Praha**, v.58, n.4, p. 187 205, 2013.

Novaes, T. E. R, Novaes ASR. Potenciais e usos medicinais do jericó, Selaginella convoluta (Arn.) Spring, no bioma Caatinga: uma breve revisão. **Research, Society and Development,** 10(1), 2021.

Oliveira C. F.; Oliveira, F. F; Oliveira, V. B; Miguel, O. G.; Miguel, M. D. Parâmetros de controle de qualidade de *Psychotria fractistipula* L.B. Sm., Klein & Delprete (Rubiaceae): Umidade, Cinzas e prospecção fitoquímica. **Revista Visão Acadêmica**, v. 15, n. 4, p. 17-23, 2014.

Paiva, I. *et al.* A2AR-induced transcriptional deregulation in astrocytes: An in vitro study. **Glia**, v. 67, n. 12, p. 2329-2342, 2019.

Pinheiro, F. V. *et al.* Decrease of adenosine deaminase activity and increase of the lipid peroxidation after acute methotrexate treatment in young rats: protective effects of grape seed extract. **Cell Biochemistry and Function: Cellular biochemistry and its modulation by active agents or disease**, v. 28, n. 1, p. 89-94, 2010.

Sá Filho, Geovan Figueirêdo de. Avaliação da indução da neuroplasticidade e do potencial antimicrobiano dos extratos metanólicos da catingueira (*Cenostigma bracteosum*) e da canafístula (*Senna trachypus*) plantas nativas da caatinga. 2022.

Santos, C.A., Ailane, M.P.R., Passos, F.C.A., Camargo, E.A., Estevam, C.S., Santos, M.R.V., Thomazzi, S.M., 2011. Antinociceptive and anti- inflammatory effects of *Caesalpinia pyramidalis* in rodents. **Rev. Bras. Farmacogn**. 21, 1077–1083, 2011.

Segal, H. P. **Technological utopianism in American culture**. Syracuse University Press, 2005.

Shelley, B.C.L. Ethnobotany and the process of drug discovery: A laboratory exercise. **The American Biology Teacher**, v.71, n.9, p.541-547, 2009.

Silva, L. N.; Trentin, D. S.; Zimmer, K. R.; Treter, J.; Brandelli, C. L. C.;Frasson, A. P.; Tasca, T.; Silva, A. G.; Silva, M. V.; Macedo, A. J. Antiinfective effects of Brazilian Caatinga plants against pathogenic bacterial biofilm formation. **Pharmaceutical Biology**, v. 53, n. 3, p. 464–468, 2015.

Silva, N.L.A.; Miranda, F.A.A.; Da Conceição, G.M. Triagem Fitoquímica de Plantas de Cerrado, da Área de Proteção Ambiental Municipal do Inhamum, Caxias, Maranhão. **Scientia Plena**, v. 6, n. 2, p. 1-17, 2010.