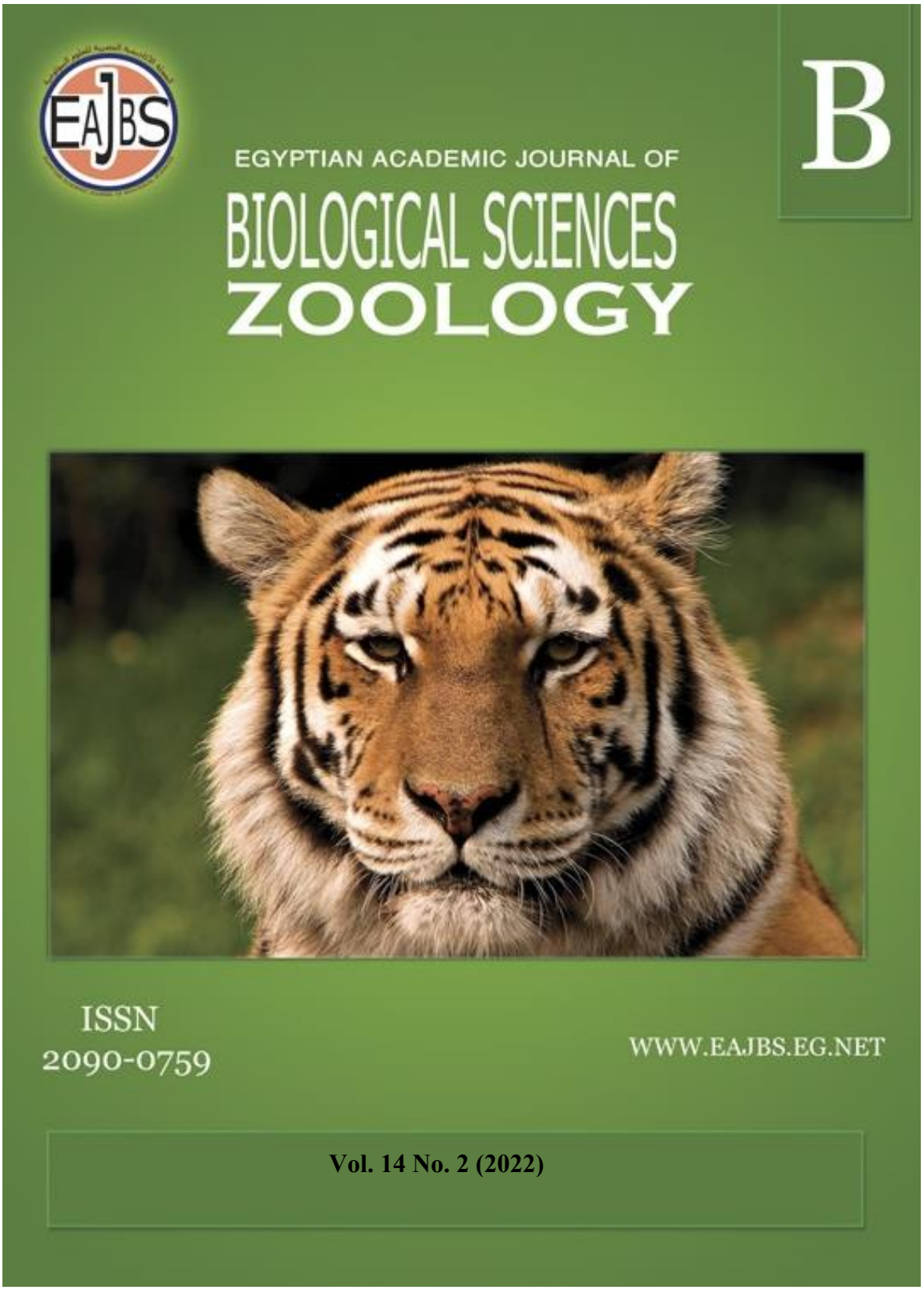

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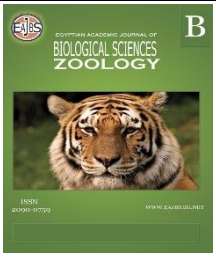
Citation: *Egypt. Acad. J. Biolog. Sci. (B. Zoology) Vol. 14(2) pp: 457-464(2022)*
DOI: 10.21608/EAJBSZ.2022.284120

Egypt. Acad. J. Biolog. Sci., 14(2):457-464(2022)

Egyptian Academic Journal of Biological Sciences
B. Zoology
ISSN: 2090 – 0759
http://eajbsz.journals.ekb.eg/



Study of the Anti-Inflammatory and Analgesic Activities of The Methanolic Extract of The Leaves of *Artemisia herba-alba* on an Animal Model

Fouzia Kheira Boukabene [1], Abdelkader Ammam* [2], Ahmed Reda Belmamoun [3], Djahida Aici [4], Abdallah Habab [5] and Chafik Mhamdia[6]

1-Laboratory of Sciences and Technics of Animal Production, Mostaghanem; Moulay Tahar University, BP 20000, Saida, Algeria.
2-Laboratory of Pharmacognosy, Bio toxicology, and Biological Valorization of Plants, Moulay Tahar University, BP 20000, Saida, Algeria.
3-Laboratory of Process, materials and environmental engineering, Djillali Liabes University, BP 22000, Sidi-Bel-Abbes, Algeria.
4- Department of Exact Sciences, Normal Higher School, BP 08000, Bechar, Algeria.
5-Mustapha Stambouli University, BP 29000, Mascara, Algeria.
6-Department of Environmental Sciences, Faculty of Natural and Life Sciences, Djilali Liabes University, BP 22000, Sidi-Bel-Abbes, Algeria.
*E. Mail: *vetokadi@yahoo.fr*

ARTICLE INFO
Article History
Received:19/9/2022
Accepted:25/11/2022
Available:2/12/2022

Keywords:
Anti-Inflammatory, analgesic, *Artemisia herba-alba*, Wistar rats, albino mice.

ABSTRACT

The use of medicinal plants of the traditional African pharmacopoeia in the treatment of various diseases has been known for a long time; the positive effects of this phytotherapy are not to be demonstrated anymore. However, it is empiricism that is at the basis of these practices. The methanoic extract of the leaves of Artemesia herba alba has analgesic and anti-inflammatory properties, which justify its traditional use. This study evaluates the anti-inflammatory and analgesic properties of the methanolic leaf extract of Artemisia herba-alba. The negative control and test groups received 40 mg/kg of the extracts. The results of the analgesic study showed a significant reduction in the number of acetic acid-induced twists compared to the control ($p<0.05$). The hot plate test showed a significant increase in the percentage of pain inhibition at 30 and 60 minutes compared to the untreated control ($p<0.05$). The extract showed a significant decrease in the pain induced by the plate test compared to the control ($p<0.05$). The anti-hematogenic effects of the extract showed a significant decrease in carrageenan-induced paw oedema at 1, 2 and 3 hours and dextran-induced inflammation compared to the control. In addition, there was an inhibition of xylene-induced ear oedema with a significant reduction compared to the control ($p<0.05$). Our extract would thus constitute an advantageous source of improved traditional medicine that is very accessible and less expensive for the population.

INTRODUCTION

Artemisia herba-alba (white wormwood) was described by the Greek historian Xenophon, as early as the beginning of the fourth century (Khireddine,2013). It is an essential fodder plant, much appreciated by livestock as a winter pasture. It has a characteristic odour of thymol oil and a bitter taste, hence its astringent character. Several names are attributed to Artemisia herba alba Asso; steppe thyme and desert wormwood. In North Africa and the Middle East, it is commonly called (chih) or (chih khersani) depending on the region. (Ayad, 2017). In Western Morocco it is also called (EL-Guesoum) (Quezel et santa, 1962) Artemisia herba aba Asso is well known since Antiquity. It is mentioned in the Bible on several occasions with the Hebrew name. Its chemical composition is completely free of alkaloids (Mechqoq,2021); the plant is rich in polyphenolic compounds, which are the best antioxidants, flavonoids and tannins. It also contains anthocyanins, phenolic acids and other substances. Phytochemical studies have shown that ivette also contains ecdysteroids, diterpenoids, iridoids and acid saponosides (Boudjelal,2013). In this regard, the aim of this research was to access its analgesic and anti-inflammatory properties.

MATERIALS AND METHODS

Plant Material and Extraction:

The plant *Artemisia herba-alba* was collected from the region of Sidi Ahmed wilaya of Saida (Algeria) in the month of December 2020. The plant was identified by Prof. Mohamed Terras teaching in the Department of Biology, University of Saida, Algeria. The aerial part of the plant was air dried and then reduced to powder. Five hundred (500) grams of powder were cold macerated in 2.5 L of methanol for 72 hours and shaken regularly. The solution was then decanted and the extract was filtered from the solution and evaporated to dryness at 40^{o}C.

Experimental Animals:

A Sixteen (16) Male Wistar albino rats weighing between (150-200 g), and 16 Swiss mice weighing between (20-30g) obtained from the Pasteur Institute (Algeria), were housed separately in plastic cages at a temperature of (23 ± 2) °C, a relative humidity of 50-55%, with a cycle of 12 hours of light / 12 hours of darkness respectively before and during the experiment. Animals were allowed access to food and water ad libitum in all experiments. The animals were handled in accordance with the standard experimental protocols approved by the Animal Ethics Committee of the Department of Biology, University of Saida.

1. Anti-Inflammatory Activity:

1.1 Carrageenan-Induced Paw Edema:

For this study, four groups of four Wistar rats (150- 200g) each were used. The extract at a dose of 40 mg/kg was administered orally to the test groups. Ten (10) mg/kg indomethacin was administered orally to the positive control group while distilled water (4 mL/kg) was administered to the negative control group. After one hour, 0.1 mL of 1% w/v carrageenan suspension in 0.9% isotonic saline was injected into the subplantar tissue of the animal's right hind paw. The thickness of the paw was measured using the Vernier calliper at 0 hours and after a 1-hour interval for 5 hours (Thambi *et al.*, 2006).

1.2 Dextran-Induced Paw Oedema:

Wistar rats weighing between 150 and 200 g were randomly divided into four groups of four animals each for this study. The test group received the extract orally, while the negative control group received distilled water (4 ml/kg) orally. The reference group

received 60 mg/kg diphenhydramine. The animals were treated for an hour before receiving an injection of 0.1 ml of 1.5% w/v dextran in 0.9% isotonic solution into the subplantar tissue of their right hind paw (Adams *et al.,* 1998). Calipers were used to measure paw thickness at 0, 1, 2, 3, 4 and 5 hours. (Bédou, 2019).

1.3 Xylene-Induced Ear Oedema:

For this study, four groups of four male Swiss albino mice were used. The extract was administered orally to the test groups. The method of Akindele *et al.* (2007) was adopted for this study. Briefly, "distilled water (4 mL/kg) was administered to the negative control group while the reference group received dexamethasone (1 mg/kg). After 30 minutes, oedema was induced in each group of mice by applying a drop of xylene to the inner surface of the right ear. Approximately 15 minutes later, the animals were sacrificed and both ears were cut and sized, and the weight was taken and recorded.

2. Analgesic Activity:

2.1 Twist Test:

Acetic acid is the most widely used chemical agent for assessing the peripheral analgesic activity of medicinal plants. Intraperitoneal (IP) injection of acetic acid causes inflammatory pain by inducing capillary permeability (Kumar *et al.,* 2010) and induces stereotypic behaviour in rats characterised by abdominal contractions. However, the acetic acid test is widely used to test the analgesic effect.

Five minutes after injection of acetic acid, painful syndromes in the rats tested appeared, characterised by stretching movements of the hind legs and twisting of the dorso-abdominal musculature.

Four groups of four male Swiss albino mice were used in this study. The test groups received the extract (40 mg/kg) orally, while distilled water (10 ml/kg) was administered to the untreated induced group (negative control). The reference drug used was aspirin (100 mg/kg). Thirty (30) minutes after the administration of the reference drug and the extract, acetic acid in normal saline (0.6% v/v) was administered to the mice by intraperitoneal injection and the torsions were counted for 30 minutes at five-minute intervals (Koster *et al.,* 1959).

2.2 Formalin Test:

Male Wistar rats were randomly separated into four groups of four animals each. The extract (40 mg/kg) was administered orally to the test group while the reference group received aspirin (100 mg/kg, subcutaneously). Distilled water was administered orally to the negative control group. 30 minutes after administration, 20µL of 1% formalin was injected subcutaneously into the right hind leg. As a sign of pain response, the time spent biting and licking the injected paw was recorded in seconds. Responses were measured for 5 minutes after formalin injection (Al-Sobarry,2012).

2.3 Hot Plate Test:

The hot plate test is one of the most widely used tests of nociception based on a high-intensity stimulus. The pain induced by the thermal stimulus must pass through the central nervous system (CNS) (Chahar *et al.,* 2012).

The jumps observed in this test involve a voluntary motor act and are considered to be unlearned and sustained by the activation of supraspinal sensory nerve circuits of a very complex organisation (Calvino, 2001).

Our Swiss mice were divided into four groups of four mice each. The animals were individually placed on a hot plate maintained at a constant temperature of 50°C, the time interval between placement and the paw shake or lick or jump was recorded as an index of response latency. The latency period before the drug was determined and recorded for each animal. The negative control group was treated orally with distilled water at 10 ml/kg. The test animal groups received the extract (40 mg/kg). Pentazocine (15 mg/kg) was

administered intraperitoneally and used as standard. The animals were placed on the hot plate at 15, 30, 45, 60 minutes, and 15 minutes after treatment and the time recorded for paw stirring or jumping was recorded.

Statistical Analysis:

The data from this study were expressed as mean ±SEM. The means of the different groups were compared by ANOVA, using the 2009 version of the Graph Pad Prism software package. P values <0.05 (95% confidence interval) were considered significant.

RESULTS AND DISCUSSION

Carrageenan-Induced Paw Edema:

Artemisia herba-alba extract at 40 mg/kg, significantly inhibited paw oedema compared to the negative control group. The 30 mg/kg extract at the first hour showed a higher level of inhibition of paw oedema compared to indomethacin. However, compared to both groups, the 40 mg/kg extract had a non-significant effect in the fourth hour but showed inhibition of paw oedema in the fifth hour (Table 1). The study examined the anti-inflammatory and analgesic potential of the methanolic extract of *Artemisia herba-alba*. As an agent for testing anti-inflammatory drugs, carrageenan proved to be an unrivalled choice due to its non-antigenic nature and the elimination of the subsequent systemic effect (Reits *et al.*, 2006). Oedema resulting from carrageenan occurs in two phases (Riahi *et al.*, 2011). The first phase occurs within one hour of carrageenan-induced inflammation and results from the release of cytoplasmic enzymes, serotonin and histamine from mast cells. Arachidonic acid metabolites and platelet activating factors also have distinct roles to play (Mbay *et al.*, 2013). The second phase of carrageenan-induced oedema occurs after one hour and is mediated by the release of proteolytic enzymes, prostaglandins, oxygen release, free radicals, arachidonate metabolites, neutrophil migration and other neutrophil-derived mediators (Abdi *et al.*, 2020) and kinins are responsible for the continuity between the two phases (Wellington *et al.*, 1987). Our results showed that the extract significantly ($p<0.05$, 0.01) inhibited paw oedema by producing an inhibitory effect in the first and second phase of inflammation. The antihistaminic potential of the extract is demonstrated in the first phase, which may be the result of the ability of the extract to reduce carrageenan-induced leakage from the microvasculature (Hotta *et al.*, 2000). Our study is in agreement with Tang *et al.* (2011). In this study performed with *Artemisia herba-alba* seeds in petroleum oil extract in albino rats, the authors reported a decrease in oedema. The potential for improvement of *C. sativa* oedema in the second phase also suggests a possible inhibition of cyclooxygenase synthesis due to the fact that the carrageenan-based inflammatory model reveals prostaglandin actions (Lalenti *et al.*, 1992).

Table 1: Effect of methanoic extract of *Artemisia herba-alba* leaves on carrageenan-induced paw oedema.

Groups	Doses (mg/kg)	Pre-drug	0hr	1hr	2hr	3hr	4hr	5hr
witness (-)	0.5 ml/kg	-	0.60±0.02	0.67±0.02	0.71±0.03	0.63±0.01	0.77±0.02	0.69±0.01
Indomethacin	10	0.36±0.02	0.49±0.04	0.51±0.03*	0.69±0.01	0.58±0.02	0.54±0.03*	0.51±0.02**
A. herba alba	40	0.33±0.01	0.55±0.02	0.53±0.03**	0.70±0.03	0.61±0.04	0.57±0.03	0.54±0.02*

Values are mean ± SEM; n=4; *=p<0.05.

Dextran-Induced Paw Oedema:

We observed that animals treated with our extract (15 and 30 mg/kg) reduced paw oedema compared to the negative control (Table 2). Furthermore, dextran-induced paw oedema is thought to be mainly mediated by serotonin and released by mast cells (Gaouji

et al., 2016). These released inflammatory mediators result in marked vascular changes such as vasodilation, increased permeability and slowed blood flow, ultimately leading to paw inflammation. Our study demonstrated that the ethanolic leaf extract of *Artemisia herba-alba* significantly ($p<0.05$, 0.01) inhibits dextran-induced paw oedema. These observations are in agreement with the study reported by Wade *et al.* (2004) where they showed that ethanolic extract of *Leptadenia arborea* demonstrated an inhibitory effect on oedema size.

Table 2: Effect of methanolic extract of *Artemisia herba-alba* on xylene-induced ear oedema in rats.

Groups	Doses (mg/kg)	Left ear (g)	Right ear (g)	Differences in both ear (g)
Witness (-)	0.5ml/kg	0.011±0.00	0.018±0.00	0.007±0.00
Aspirin	100	0.062±0.01	0.087±0.02	0.025±0.02***
A. herba alba	40	0.069±0.01	0.102±0.0	0.033.01**

Values are mean ± SEM; n=4; **p<0.05.

Xylene-Induced Ear Oedema:

Our extract (40 mg/kg) inhibited xylene-induced ear oedema compared to the negative control. The xylene-induced ear oedema method is used to assess anti-inflammatory steroids and is less sensitive to non-steroidal anti-inflammatory agents (Israa *et al.,* 2019). The indicators of acute inflammation after topical applications of xylene detected were: inflammatory cell infiltration, severe vasodilation and oedematous changes in the skin. This study showed that xylene-induced ear oedema was inhibited. Our results corroborate with the study conducted by Okpo and *et al.* (2001) where they demonstrated the inhibitory potential of *Crinum glaucum* in xylene-induced ear oedema.

Table 3: Effect of ethanolic extract of *Artemisia herba-alba* leaves on acetic acid-induced spasm as a function of time.

Groups	Doses (mg/kg)	0-5 mins	5-10 mins	10-15 mins	15-20 mins	20-25 mins	25-30 mins
witness (-)	0.5 ml/kg	17.0±6.09	26.9±2.10	26.0±2.38	19.8±3.27	18.0±2.58	15.3±1.19
Aspirin	100	7.15±1.32*	19.0±1.00**	21.5±1.56	20.5±1.26	17.4±2.18	15.4±1.18
Artemesia hh	30	0.0±0.0**	15.3±1.96***	15.0±2.16**	10.50±1.94**	8.51±2.18*	7.50±1.14***

Values are mean ± SEM; n=4; p<0.05.

Mouse Torsion Test:

The nociceptive response is shown in the table, indicating the number of cramps made by the animal following intraperitoneal injection of acetic acid, its standard deviation and the percentage of cramp inhibition. The results of this test show that the number of cramps induced by acetic acid was significantly (p<0,001) reduced by the extracts of our studied plant. We noticed this effect to a greater extent than that of the reference (Aspirin). And has a maximum antinociceptive activity.

In comparison with the results of the study conducted by Reanmongkol and Itharat (2007), the extract of *Hibiscus sabdariffa calyces L* at 400mg/kg inhibited the number of twists by 7.8%, which is largely inferior to the results obtained in our study.

Table 4: Effect of ethanolic leaf extract of *Artemisia herba-alba* on hot plate induced pain as a function of time.

Groups	Doses (mg/kg)	0 sec	15 mins	30 mins	45 mins	60 mins
witness (-)	0.5 ml/kg	3.00±0.32	4.27±0.75	3.20±0.22	3.10±0.34	2.87±0.46
Pentazocine	100	2.15±0.13	6.75±2.00*	7.40±1.82**	10.92±0.89***	9.90±1.68***
A.herba alba	40	3.70±0.43	6.12±2.57	5.70±2.38*	8.15±1.79**	8.14±1.79**

Values are means ± SEM; n=4; p<0.05

Formalin Test:

In the formalin-induced test, the extract improved formalin-induced pain compared to the negative control group. This observed reduction was seen in both phases. The 40 mg/kg dose had an effect in both phases similar to that of aspirin.

One of the most widely used methods for assessing anti-nociceptive activity is an acetic acid-induced twisting of animal models (Gene *et al.,* 1998). This method is very sensitive, even at lower doses, compared to the tail-prick test for detecting the anti-nociceptive potential of bioactive agents (Bouhanika *et al.,* 2019). Our study showed that the extract caused a significant reduction in acetic acid-induced biting at all doses. The extract was generally more effective than the 100mg/kg dose of aspirin, which was the control drug used, and was maintained throughout the 30-minute period, suggesting peripheral mediation for the analgesic effect of the extract.

Hot Plate Test:

When compared to the control group, the extract reduced the amount of time that mice were in discomfort after being placed on a hot plate (Table 4). Pentazocin (15mg/kg), a medication recognized for its central activity, showed a stronger inhibiting impact than the groups who received extract treatment. Based on the fact that central analgesics like tramadol increase the pain threshold by inhibiting the formation of prostaglandins, hot plate studies were conducted (Ibrahim et al, 2012). However, additional anti-nociceptive processes may have allowed the extract to operate. In fact, activating K+-ATP channels that allow the buildup of intracellular Ca++, which in turn starts a cascade of secondary messengers, can prevent thermal hyperalgesia (Chen *et al.,* 2012). Our results revealed that the extract considerably increased the latency duration in the hot plate experiment, indicating that the central nervous system had a major role in mediating this analgesic effect. The analgesic effect reported in this study is considered in comparison to earlier studies (Mio *et al.,* 2002) where rats treated with an aqueous extract of *Balbisia calycina* at a concentration of 400 mg/kg did not affect the latency duration.

To evaluate centrally mediated nociceptive effects, hot plate experiments are frequently employed (Newfel et al; 2021). In our study, we observed that our extract was able to induce a significant extension of the pain response latency on the hot plate, as shown in Table 4, suggesting that the analgesic activity was centrally mediated. The abnormal calmness observed a few minutes after the administration of the extract in the animal models suggests the psychotropic effects of the extract.

Conclusion

The multitude of pharmacological effects established during this work, allowing to justify and confirm the traditional therapeutic indications based on *Artemisia herba alba.* We have also confirmed the traditional preparations that can be proposed in therapeutics as analgesic and anti-inflammatory as acetylsalicylic acid would constitute an advantageous source of traditional medicine very accessible and less expensive to the populations. and constitutes a basis for other studies aiming at investigating the mechanisms of action as well as the synergy in toxicity that in pharmacology.

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