ORIGINAL ARTICLE

sciendo

10.2478/AMB-2024-0060

EXPLORING THERAPEUTIC POTENTIAL OF MALCOLMIA AEGYPTIACA SPR. AND MATTHIOLA LIVIDA DC. EXTRACTS IN RAT MODELS USING HOT-PLATE, WRITHING AND CARRAGEENAN-INDUCED PAW EDEMA TESTS

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Abstract. Background: *Malcolmia aegyptiaca (locally known as El Harra) and Matthiola livida (locally known as Chegara) are medicinal plants traditionally used to relieve pain and reduce inflammation. Little is known about the flavonoid content or the analgesic and anti-inflammatory properties of these plants.* ***Aims:*** *The aim of the study was to explore the natural therapeutic potential of two xerophytic plants, M. aegyptiaca Spr. and Matthiola livida DC., for analgesic and anti-inflammatory activities using hot-plate, writhing and carrageenan-induced paw edema tests.* ***Materials and Methods:*** *Flavonoid content was quantified using the AlCl3 as reagent. Analgesic activity was assessed using hot-plate (in concentrations of 30 to 80 mg/kg) and writhing tests (20 and 40 mg/kg) in the rats treated. Anti-inflammatory activity was evaluated using the carrageenan-induced paw edema model in rats treated with two doses (25 and 50 mg/kg) of the two plant extracts.* ***Results:*** *M. livida extract had a higher flavonoid concentration compared to M. aegyptiaca extract. Both the M. aegyptiaca and M. livida extracts exhibited dose-dependent analgesic effects in the hot-plate test, with higher doses inducing a stronger and more sustained analgesia. M. aegyptiaca extract displayed weaker dose-dependent anti-nociceptive effects in the writhing test compared to the standard NSAID indomethacin. The anti-nociceptive effects of the M. livida extract were mainly observed at the higher dose in the writhing test. Both extracts demonstrated dose-dependent anti-inflammatory activity in the carrageenan-induced paw edema model, with higher doses exhibiting greater inhibition at later time points.* ***Conclusion:*** *The M. aegyptiaca and M. livida methanolic extracts possess analgesic and anti-inflammatory properties, supporting their traditional use for the pain and inflammation management. Further research is needed to elucidate the active components and mechanisms of action responsible for these activities.*

Key words: *Malcolmia aegyptiaca Spr. (El Harra), Matthiola livida DC. (Chegara), hot-plate test, writhing test, carrageenan-induced paw edema test*

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Received: *10 January 2024;* ***Revised:*** *24 April 2024;* ***Accepted:*** *22 August 2024*

INTRODUCTION

Chronic and acute pain affect millions worldwide, significantly impacting quality of life [1]. Existing analgesics, including opioids, often come with drawbacks like addiction, intolerance, and adverse effects [2]. Consequently, the search for safer and more effective pain management solutions continues. Traditional medicine utilizes various plants for pain relief, offering a rich source of potentially active compounds [3].

Malcolmia aegyptiaca Spr., also known as El Harra in Algeria, is a small flowering plant. It is native to North Africa and the Arabian Peninsula, where it thrives in rocky terrains and arid environments. *M. aegyptiaca* is a slender annual or biennial plant reaching a height of up to 30 cm. It has delicate, feathery foliage and produces clusters of small, four-petal flowers at the tip of its stems [4]. The flowers vary in color from white and yellow to lavender and purple, adding a splash of vibrancy to the often harsh landscapes it inhabits [4].

Matthiola livida DC., commonly known as Chegara, is a small annual flower usually reaching a height of 30-50 cm; it thrives in the harsh, rocky landscapes of North Africa and the Middle East [5].

Malcolmia aegyptiaca and *Matthiola livida*, the members of the Brassicaceae family, exhibit diverse medicinal potentials. These plants have demonstrated antioxidant, anti-inflammatory, and anti-cancer properties, potentially contributing to enhancement of the cardiovascular and digestive health [6].

The hot-plate test highlights a patient sensitivity to thermal pain, which is often associated with neuropathic conditions such as diabetic neuropathy or spinal cord injuries [7]. By comparing latency before and after hot-plate treatment, physicians can measure the effectiveness of pain management strategies, including medications, nerve blocks, or neuro-modulation therapies [8].

Writhing test mimics the discomfort of visceral pain, often experienced in conditions like intestinal cramping, pancreatitis, or menstrual cramps [9]. Evaluating the effect of analgesics on writhing responses helps predict their efficacy in managing internal pain. This can guide treatment decisions for patients suffering from visceral pain conditions.

Carrageenan-induced paw edema test models inflammatory pain, a major component of conditions like arthritis, tendonitis, and post-surgical pain [10]. By measuring the reduction in paw edema following the drug or extract administration, researchers can gauge their anti-inflammatory potential and predict their effectiveness in managing inflammatory pain conditions.

To avoid drug toxicity and search for alternative, non-toxic and effective sources, the study aimed to evaluate the analgesic effects of the methanolic extracts of *M. aegyptiaca* and *M. livida* in two established pain models in rats – the hot-plate test for thermal nociception and the writhing test for visceral pain, and the anti-inflammatory effects of the methanolic extracts of *M. aegyptiaca* and *M. livida* by carrageenan-induced paw edema as a test for inflammatory pain.

MATERIALS AND METHODS

Plant material

The aerial parts of *Malcolmia aegyptiaca* and *Matthiola livida* were collected in March 2021 on the territory of El Oued Province (33.45644609569057 N, 6.811382715116063 E), Southeastern Algeria. Plant samples were washed with cold running water to remove any debris. Then, they were dried in the dark, ground into a fine powder, and stored for further use.

Preparation of crude methanolic extracts

50 grams of the dried plant material were soaked in 500 mL of 99% methanol at room temperature in darkness for 24 hours. Subsequently, the solution was filtered, and the solvent was removed by evaporating it to dryness using a rotary evaporator (type Buchi R-200) at 50 °C to obtain the crude methanolic extracts [11].

Estimation of total flavonoid content

The procedure described by Ben Ali et al. [12] was employed to identify flavonoids. Detection involved the use of metallic magnesium and hydrochloric acid, resulting in a positive outcome. Subsequently, we adopted the method followed by Chouikh et al. [13] in quantitative evaluation, which involved combining 0.5 mL of the initial methanolic plant extract with 0.5 mL of a 2% AlCl3 solution after a 15-minute interval. The absorbance at 430 nm using a UV-Vis spectrophotometer (type Shimadzu) was then gauged to quantify the flavonoid content in milligrams of quercetin equivalent (QE) per gram of extract (mg QE/g Ex).

Acute toxicity

The research was conducted on male rats with weights ranging from 140 to 160 grams, sourced from the central pharmacy farm of Tunis (SIPHAT). Throughout the experimental period, the animals were subjected to treatment adhering to ethical guidelines intrinsic to animal experimentation.

Thirty mice underwent a 24-hour fasting period. Afterward, they were split into eight groups, each composed of three mice. These groups were then categorized into four subgroups based on the type of the methanolic plant extract used. Every subgroup received oral doses of either *M. aegyptiaca* or *M. livida* extract, prepared in a 1% solution of carboxymethyl cellulose. The doses administered ranged from 300 to 1000 mg/kg, aiming to examine potential alterations in behavior, neurological functions, and independence. Additionally, mouse mortality was monitored 24 and 72 hours post drug administration using the Whalum method [14].

Experimental protocol

The rats were divided into 6 groups of 6 subjects each: The first group received distilled water (control negative group). The second group (control positive group) received a solution of the medication (Paracetamol or Indomethacin). The third and fourth groups received the extract of *M. aegyptiaca* (20 to 60 mg/kg of body weight). The fifth and sixth groups received the extract of *M. livida* (20 to 80 mg/kg of body weight).

Hot-plate test

The hot-plate test was determined according to the method reported by Tchekalarova et al. [15]. Briefly, in the day of the experiment, the animals (n = 6) were intraperitoneally (i.p.) injected with 0.2 mL normal saline (control group, 0.9%, w/v), paracetamol 10 mg/kg (positive control) and 40 and 80 mg/kg of extract of *M. livida*/ 30 and 60 mg/kg of extract of *M. aegyptiaca* (test sample groups), respectively. 30 min later, the rats were placed for 30 sec on a hot-plate heated at 55°C, and the time (in seconds) between placement and licking of their hind paws or jumping was recorded as the response latency. The cut-off time was 30 s. The reaction time was recorded at zero time, 60 and 120 min after the extract administration.

Writhing test

The acetic-acid writhing test was used to evaluate the analgesic activity [16] for both extracts. Four groups of mice (n = 6 per group) were injected i.p. with 0.1% acetic acid (10 mL/kg body weight), and the intensity of nociception was quantified by counting the total number of writhes over a period of 30 min. The animals received two doses of extracts (20 and 40 mg/kg) or sterile saline (control group, 0.9%, w/v) 30 min before acetic acid injection. Indomethacin (10 mg/kg) was used as a reference substance (positive control).The numbers of writhes were counted 5 min after acetic acid injection for a period of 30 min. Percentage inhibition of writhing was calculated using the following formula:

$$\% \text{ inhibition} = [\text{Mean number of writhing (control)} - \text{Mean number of writhing (test)} / \text{Mean number of writhing (control)}] \times 100.$$

Carrageenan-induced paw edema

The animals were randomly divided into 6 groups (n = 6), and edema was induced by the injection of 50 µL of a suspension of carrageenan (1% in sterile saline) in the plantar side of right hind paws of the mice (group 1). The mice were pretreated intraperitoneally (i.p.) with either 0.9% NaCl (group 2, untreated control), 10 mg/kg Indomethacin (group 3, reference control), or 25 and 50 mg/kg of extracts (groups 4 and 5, respectively) half hour before carrageenan injection. Paw volume was measured with a plethysmometer (Ugo Basile 7140) immediately before (Vo), and at 60, 180 and 300 min after carrageenan treatment (Vt). Inhibitory activity was calculated as previously described by Jude et al. [17], according to the following formula:

$$\% \text{ inhibition of edema} = [(Vt\text{-}Vo) \text{ Control} - (Vt\text{-}Vo) \text{ Treated} / (Vt\text{-}Vo) \text{ Control}] \times 100.$$

Where:

(Vt-Vo) Control is edema produced in the control group; (Vt-Vo) Treated is edema produced in the treatment group.

Statistical analysis

All experiments were conducted independently in triplicates and the data are expressed as mean ± standard deviations. All data were analyzed statistically using one-way analysis of variance (ANOVA). Difference was considered statistically significant at $p \geq 0.05$.

RESULTS

Quantitative evaluation of flavonoid content of M. aegyptiaca and M. livida methanolic extracts

In the figure below, it can be observed that the flavonoid concentration in the *M. livida* extract is higher than the *M. aegyptiaca* extract (1.97 mg QE/g Ex vs. 1.86 mg QE/g Ex, respectively). The difference suggests that the *M. aegyptiaca* extract contains a higher amount of flavonoids, a group of plant compounds, which possess antioxidant and anti-inflammatory properties.

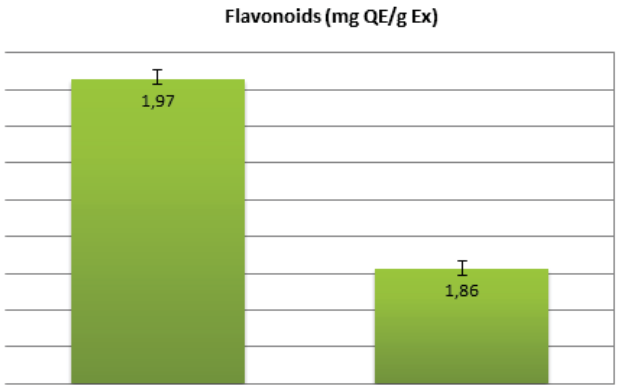

Fig. 1. Flavonoid contents of *M. aegyptiaca* (left) and *M. livida* (right) methanolic extracts.

Acute toxicity

In the acute toxicity evaluation, it was noted that both extracts demonstrated safety at all concentrations tested, including the maximum dose of 1000 mg/kg, resulting in no deaths among the subjects under investigation. These data also allowed the selection of different therapeutic doses.

Hot-plate test

The response latencies of the control group remained relatively stable over time, suggesting no significant changes in pain sensitivity. The paracetamol group displayed a marked increase in response latency at all-time points, indicating a robust analgesic effect (Table 1).

Both paracetamol and the methanolic extract of *M. aegyptiaca* demonstrated significant analgesic effects in the hot-plate test, as indicated by their significantly higher response latencies compared to the control group at various time points ($p < 0.001$) (Table 1).

The extract of *M. aegyptiaca* exhibited a dose-dependent analgesic effect, with the 60 mg/kg dose producing a greater response latency than the 30 mg/kg dose at all time points. The analgesic effect of paracetamol was sustained throughout the 120-minute observation period, while the effect of the extract of *M. aegyptiaca* appeared to diminish slightly over time, particularly at the lower dose.

The 30 mg/kg dose of the extract produced a significant analgesic effect at 0 minutes, but this effect waned at 60 and 120 minutes. The 60 mg/kg dose demonstrated a stronger and more sustained analgesic effect, with significant differences from the control group observed at all time points.

The results suggest that the methanolic extract of *M. aegyptiaca* possesses analgesic properties that may be comparable to those of paracetamol.

Table 1. Effects of methanolic extracts of *M. aegyptiaca* and *M. livida* on hot-plate test in rats.

Treatment	Dose mg/kg	Reaction latency (s)		
		0 min	60 min	120 min
Control group	Normal saline	1.76 ± 0.45	2.24 ± 0.19	1.12 ± 0.44
Paracetamol	10 mg/kg	4.80 ± 0.36 ***	5.64 ± 0.81 ***	5.36 ± 1.00 **
Methanolic extract of *M. aegyptiaca*	30 mg/kg	6.14 ± 1.29 ***	3.12 ± 0.35	2.42 ± 0.14 ***
	60 mg/kg	9 ± .0.46 ***	5.32 ± 0.43 ***	4.62 ± 0.64 ***
Methanolic extract of *M. livida*	40 mg/kg	5.72 ± 0.29 ***	6.08 ± 0.63 ***	3.4 ± 0.25 ***
	80 mg/kg	6.72 ± 0.23 ***	7.34 ± 0.26 ***	5.78 ± 0.6 ***

Values are expressed as mean ± SEM. (n = 6).

*** Significantly different at $p < 0.001$ when compared to control.

The methanolic extract of *M. livida* demonstrated significant analgesic properties in the hot-plate test (Table 1), comparable to those of paracetamol. The extract displayed a dose-dependent effect, with the 80 mg/kg dose producing a greater analgesic response than the 40 mg/kg dose. The analgesic effect of the extract was sustained over time, with significant differences compared to the control group observed at all time points for the 80 mg/kg dose.

A dose of 40 mg/kg showed a significant analgesic effect at 0 and 60 minutes, but not at 120 minutes. A dose of 80 mg/kg showed a significant analgesic effect at all time points, with a more pronounced effect at 60 and 120 minutes.

A dose of 80 mg/kg appears to be more effective and provides a more sustained effect. Results indicate that the methanolic extract of *M. livida* possesses analgesic properties, which require further research for potential use in pain management.

Writhing test

In the control group, the average number of squirms remained high, indicating a significant pain response. On the other hand, in the indomethacin group, a significant decrease in squirms, which indicates its strong analgesic effect, was observed (Table 2).

The methanolic extract of *M. aegyptiaca* demonstrated anti-nociceptive activity in the writhing test (Table 2). The effect of the extract was dose-dependent and significantly weaker than that of indomethacin, a standard NSAID. In the group treated with 20 mg/kg extract of *M. aegyptiaca*, a moderate decrease in writhes was observed, with a statistically significant difference ($p < 0.01$) compared to the control group.

In the group treated with 40 mg/kg extract of *M. aegyptiaca*, a substantial reduction in writhes was observed, with a statistically significant difference ($p < 0.001$) compared to the control group and a 50.60% inhibition of writhing. The *M. aegyptiaca* extract may possess anti-nociceptive properties and could be potentially useful for pain management, but its efficacy is lower than standard NSAIDs like indomethacin.

Table 2. Analgesic effects of methanolic extracts of *M. aegyptiaca* and *M. livida* on acetic acid induced writhes.

Treatment	Dose	Number of writhes (30 min)	Inhibition (%)
Control (acetic acid 0.1%)	10 mL/kg	27.66 ± 1.5	-
Indomethacin	10 mg/kg	10 ± 1.89***	63.85
Methanolic extract of *M. aegyptiaca*	20 mg/kg	20.33 ± 1.63**	26.50
	40 mg/kg	13.66 ± 2.5 ***	50.60
Methanolic extract of *M. livida*	20 mg/kg	25.33 ± 5.08*	19.14
	40 mg/kg	13.16 ± 2.63 ***	57.97

*Significantly different at $p < 0.05$ when compared to control.

**Significantly different at $p < 0.01$ when compared to control.

The methanolic extract of *M. livida* demonstrated anti-nociceptive activity in the writhing test, but only at the higher dose of 40 mg/kg (Table 2). The effect of the extract was significantly weaker than that of indomethacin. In the group treated with 20 mg/kg extract of *M. livida*, a slight decrease in writhes was observed, but the difference from the control group was only statistically significant at $p < 0.05$, indicating a weak effect. In the group treated with 40 mg/kg extract of *M. livida*, a substantial reduction in writhes was observed, with a statistically significant difference ($p < 0.001$) compared to the control group and a 57.97% inhibition of writhing. The *M. livida* extract may possess anti-nociceptive properties, but its efficacy appears to be dose-dependent and lower than established NSAIDs like indomethacin.

Both the *M. aegyptiaca* and *M. livida* extracts showed dose-dependent anti-nociceptive effects in the writhing test. The *M. aegyptiaca* extract seemed slightly more potent than the *M. livida* extract at both doses.

Carrageenan-induced paw edema

In the control group, paw edema developed significantly over time, indicating a strong inflammatory response. In the indomethacin group, a significant decrease in paw edema was observed at all time points, indicating its strong anti-inflammatory effect (Table 3).

The methanolic extract of *M. aegyptiaca* demonstrated anti-inflammatory activity in the carrageenan-induced paw edema model in rats (Table 3). The effect was dose-dependent, with the 50 mg/kg dose producing significantly higher inhibition of paw edema compared to the 25 mg/kg dose at all time points (60, 180, and 300 minutes). The anti-inflammatory activity of the extract was lower than that of indomethacin. While indomethacin showed inhibition percentages above 50% at all time points, the extract reached this level only at the 50 mg/kg dose and only at the 60-minute time point.

In the group treated with 25 mg/kg extract of *M. aegyptiaca*, a moderate, however, statistically significant reduction in paw edema was observed at all time points compared to the control group. In the group treated with 50 mg/kg extract of *M. aegyptiaca*, a more substantial reduction in paw edema was observed at all time points, with statistically significant differences compared to both the control group and the 25 mg/kg extract group. These results are promising for the potential anti-inflammatory properties of the *M. aegyptiaca* extract.

Table 3. Anti-inflammatory effect of methanolic extracts of *M. aegyptiaca* and *M. livida* on carrageenan-induced paw edema in rats.

Treatment	Dose	Inhibition (%)		
		60 min	180 min	300 min
Control (carrageenan 1%)	10 mL/kg	–		
Indomethacin	10 mg/kg	70.31	50.67	55.66
Methanolic extract of *M. aegyptiaca*	25 mg/kg	23.45	31.24	36.64
	50 mg/kg	51.23	48.75	47.52
Methanolic extract of *M. livida*	25 mg/kg	45.63	44.12	54.42
	50 mg/kg	53.47	60.14	52.22

The methanolic extract of *M. livida* demonstrated anti-inflammatory activity in the carrageenan-induced paw edema model in rats (Table 3). The effect was dose-dependent, with the 50 mg/kg dose producing significantly higher inhibition of paw edema at 180 minutes compared to the 25 mg/kg dose. The anti-inflammatory activity of the extract was weaker than that of indomethacin at all time points, despite reaching a similar inhibition percentage at 180 minutes with the 50 mg/kg dose.

In the group treated with 25 mg/kg extract of *M. livida*, a moderate yet statistically significant reduction in paw edema was observed at all time points compared to the control group. In the group treated with 50 mg/kg extract of *M. livida*, a slightly higher reduction in paw edema was observed at all time points, with a statistically significant difference at 180 min-

utes compared to the 25 mg/kg dose. Notably, 60% inhibition at 180 minutes was achieved at this dose.

Both extracts exhibited dose-dependent anti-inflammatory effects. The *M. livida* extract showed slightly higher inhibition percentages at later time points (180 and 300 minutes) with the 50 mg/kg dose compared to the *M. aegyptiaca* extract. However, because of the limited data, further research is needed to confirm this potential difference.

DISCUSSION

In a research investigation conducted by Zeghoud et al. [18], it was observed that the flavonoid concentration in *M. aegyptiaca* varied from 0.75 to 2.93 mg/g, whereas, in *M. livida*, it ranged from 1.24 to 2.78 mg/g.

Flavonoids, natural compounds found in plant-based foods, play a versatile role in managing pain and inflammation through several mechanisms [19]. Flavonoids scavenge free radicals, reducing oxidative stress and inflammation [19]. They inhibit enzymes involved in the production of pro-inflammatory mediators like prostaglandins and leukotrienes. Their anti-inflammatory activity can ease the pain associated with various conditions like arthritis, muscle soreness, and headaches [20]. Flavonoids interact with cellular signaling pathways involved in pain perception and inflammation. They can inhibit NF-κB, a key transcription factor for inflammatory genes, further reducing inflammation [19]. Certain flavonoids, like quercetin, have been shown to potentiate the effects of conventional pain medications like NSAIDs [20].

Different flavonoids possess unique properties targeting various aspects of pain and inflammation. For example, curcumin (from turmeric) exhibits potent anti-inflammatory and pain-relieving effects [21], while apigenin (found in parsley and chamomile) shows promise in managing neuropathic pain [22].

The hot-plate test is a widely accepted model for evaluating neuropathic pain. Central analgesics can prolong reaction times in this test, because they act primarily at the spinal cord level [23]. The results obtained in the hot-plate test indicate that central analgesic agents can be effective in relieving nerve pain.

The writhing test, induced by acetic acid, is used to assess peripherally acting pain-relieving medications. Pain is triggered indirectly through internal agents such as prostaglandin, which stimulate sensory nerves in the peripheral nervous system [24]. Elevated prostaglandin levels within the abdominal cavity amplify inflammatory pain by increasing the permeability of capillaries [24].

In the writhing test, when compared to native plants, a prior study by Chouikh et al. [25] indicated that the methanolic extract of Calligonum comosum exhibited an estimated inhibition of 45.82% at a concentration of 100 mg/kg. Additionally, Chouikh [26] found that the methanolic extract of Ephedraalata showed an estimated inhibition of 30.7% at a concentration of 50 mg/kg. This highlights a preference for the methanolic extracts of *M. aegyptiaca* and *M. livida*, as their inhibition values surpassed 50% at a concentration of 40 mg/kg.

Carrageenan-induced paw edema is a widely used model for studying inflammation. The inflammatory process triggered by carrageenan injection involves a complex cascade of events: Carrageenan activates mast cells, specialized immune cells, leading to the release of inflammatory mediators like histamine, leukotrienes, and prostaglandins [27]. These mediators cause vasodilation and increased vascular permeability enabling fluid and inflammatory cells to infiltrate the tissue resulting in swelling (edema). [28]

In a prior investigation, the 80% methanol extract of Achillea odorata plant [29] exhibited a slight advantage over the two methanol extracts being examined. However, the latter demonstrated superiority compared to the methanol extract of Calligonum comosum [30].

The findings regarding the methanolic extracts of *M. aegyptiaca* and *M. livida* plants offer several potential benefits. These extracts demonstrate analgesic and anti-inflammatory properties, offering potential alternatives to existing medications based on synthetic compounds. Thus, the reliance on medications with potential side effects is reduced. Development of natural pain and inflammation management options with potentially milder side-effect profiles can lead to improved patient choice and quality of life.

M. aegyptiaca and *M. livida* extracts may act through different mechanisms compared to traditional medications, providing new insights into the pain and inflammation pathways, potential for targeting different aspects of pain and inflammation, leading to more effective treatments and development of combination therapies with the existing medications for synergistic effects.

These initial findings pave the way for further research on:

- Isolating and identifying the active compounds responsible for the observed effects.
- Elucidating the precise mechanisms of action of these extracts.

- Optimizing extraction and formulation methods for improved efficacy and delivery.
- Conducting preclinical and clinical trials to establish safety and efficacy in the treatment of specific pain and inflammation conditions.

However, it is important to note that these results were obtained in animal models. Additional research is needed to confirm these findings in humans.

CONCLUSION

This study aimed to investigate the analgesic and anti-inflammatory activities of the extracts of two Saharan plants, *M. aegyptiaca* and *M. livida*. The extracts derived from *M. aegyptiaca* and *M. livida* showed notable anti-nociceptive and anti-inflammatory characteristics across various pain and inflammation models. These effects were contingent on dosage, indicating that higher doses elicit stronger responses. Nevertheless, the effectiveness of the extracts was lower compared to established medications such as indomethacin. The outcomes yielded by the *M. aegyptiaca* and *M. livida* extracts exhibit considerable promise in the pursuit of developing innovative, natural and potentially safer methods for managing pain and inflammation. *M. aegyptiaca* and *M. livida* methanolic extracts possess analgesic and anti-inflammatory properties, supporting their traditional use for pain and inflammation management. Further research is required to elucidate the active components and mechanisms of action responsible for these activities. Moreover, further comprehensive research is imperative to fully utilize their natural therapeutic potential.

Conflict of Interests Statement

There are no conflicts of interest declared by the authors.

Acknowledgments

The authors state that this study was executed and funded by the Laboratory of Biology, Environment and Health (LBEH) at the El Oued University, Algeria.

This study is a part of the PRFU project D01N01UN390120220003.

Authorship contribution statement

1. ***CHOUIKH Atef:*** *Investigation, methodology and supervision.*

2. ***BEN ALI Anis:*** *Investigation and writing.*

3. ***BOUSBIA BRAHIM Aida:*** *Supervision assistant and proofreading.*

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