The *in vivo* evaluation of antinociceptive and antipyretic activities of *Marrubium deserti* De Noé infusion extract

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The aim of this study was to evaluate the *in vivo* antinociceptive and antipyretic activities of *Marrubium deserti* De Noé infusion extract. Antinociceptive effect was evaluated by acetic acid induced writhing response, formalin-induced paw licking and the hot plat method in mice, while antipyretic activity was tested by brewer's yeast induced pyrexia in rats. In each test, we examined the doses of 250, 500 and 1000 mg/kg body weight (bw) of the extract. The infusion extract produced dose-dependent antinociceptive effect against chemically and thermally induced nociceptive pain stimuli in mice. In acetic acid induced writhing test, the inhibition percentage of writhing response was 49.12% at 1000 mg/kg bw ($p<0.001$). This extract also significantly ($p<0.001$) inhibited the licking response of the formalin test at 1000 mg/kg bw in both the early phase (64.39%) and the late phase (70.75%). In the hot plate method, the infusion extract significantly ($p<0.001$) increased the reaction time to heat sensation to 58.21% at 1000 mg/kg bw Moreover, the extract possessed an excellent ($p<0.001$) antipyretic effect and even better than the reference drug. These findings indicate that *M. deserti* De Noé infusion extract possesses antinociceptive and antipyretic activities which could be due to the presence of bioactive compounds in this plant.

Keywords: *M. deserti*, Infusion, Phytochemical screening, Acute toxicity, Antinociceptive, Antipyretic

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Pain is defined as an unpleasant sensory and emotional experience associated with tissue damage[1-2]. Analgesics are the substances which decrease pain sensation by increasing pain threshold to external stimuli[3]. The Non Steroidal Anti-Inflammatory Drugs (NSAIDs) are among the most widely used of all therapeutic agents. They are useful in the treatment of pain and some inflammatory diseases. However, long-term use of the NSAIDs has been associated with gastrointestinal ulceration, bleeding and nephrotoxicity[4-5]. Therefore, the investigation of new analgesics agents are still a challenge for medical community. As a result more people are turning to herbal medicines for alternative treatment of pain. Herbal drugs have fewer side effects and are largely required as substitute therapeutics[6].

Traditional medicine is a combination of knowledge and practice, used in diagnosing, preventing and eliminating several diseases. It may rely on past experience and observation handed down from generation to generation verbally or in writing.

Preservation of this information can be a valuable policy for good usage of natural sources. Lamiaceae family has been holding a place of value for hundreds of years due to the numerous aromatic species which used as components of various herbal treatments[7]. The genus *Marrubium* is represented by 97 species which are widely spread over the temperate and warm regions. *Marrubium* species are indigenous in Europe, the Mediterranean area and in Asia[8-10]. Among them, *Marrubium deserti* De Noé known as Merriouet saharaui or Djaîdis an endemic herb of central and north Algerian Sahara growing in dry pastures. This plant is a shrub with blancher's leaves and stems. The leaves are velvety and opposite, and are generally terminated by three large teeth of variable forms. The flowers are pale pink[11]. In Algerian traditional medicine, the leaves and the young buds of *M. deserti* are used in the form of a decoction as a remedy for respiratory diseases like fever, diabetes and as diuretic[12]. Furthermore, it is frequently used in traditional medicinal for treating digestive disorders as antispasmodic and as local treatment against scorpion stings and in case of allergy[10,13].

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The biological activities of many *Marrubium* species and their components are reported and it has been showed to possess antinociceptive[14-15], antioxidant[16-19], antimicrobial[20], antifungal, cytotoxic[21], antioedematogenic[22], hypolipidemic, hypoglycemic[23], hepatoprotective[24], antiproliferative[25], vasorelaxant[26] and anti-inflammatory effects[27].

The essential oil from aerial parts of *M. deserti* De Noé, obtained by hydro-distillation, was analyzed by Gaz Chromatography (GC) and Gaz Chromatography - Mass Spectrometry (GC-MS). Thirty-seven compounds were identified in the oil, with germacrene-D, as the major component (45.7%). This oil was characterized by significant hydrocarbon fraction (78.1%) and the predominance of sesquiterpenes (67.4%)[28].

The best known and first isolated diterpenoid was obtained from *M. vulgare* in 1842. It was characterized as marrubiine. This furanie labdane diterpene is, in part, responsible for therapeutic properties of *Marrubium* sp. The genus *Marrubium* is a rich source of diterpenoids, flavonoids and phenylethanoid glycosides[29].

The purpose of the present study was to evaluate the antinociceptive and antipyretic activities of the infusion extract from *M. deserti*'s aerial parts in animal models in order to establish a probable mechanism of action and to justify the traditional uses of this plant. The acute toxicity study of the plant was also carried out.

Materials and Methods

Plant Material

Aerial parts of *M. deserti* De Noé were collected from Ain Zaatout town (Biskra, northeast of Algeria) in 2012. The plant species has been identified based on the flora of Quezel and Santa[11] and according to the validation of the national institute of the forestry research (INRF), Tamanr asset, Algeria. A voucher specimen of *M. deserti* De Noé (N° 5821-PAM/LRZA/USTHB) has been deposited at the Laboratory of Research on Arid Zones (LRZA), Algiers, Algeria.

The aerial parts were dried and pulverized to powder and preserved for further studies. The infusion extract was prepared according to the traditional method; the fine powder was dissolved in boiling normal saline water (0.9% NaCl). The filtrate was used for biological tests on animals at different doses.

Animals

Wistar rats (*Rattus norvegicus*) (160-200 g) and *Albino* mice (*Mus musculus*) (25±5 g) of both sexes were procured from Pasteur institute, Algiers, Algeria. Animals were housed in plastic cages at the temperature of 24±2°C and 50±5% relative humidity, with a 12 light/dark cycle respectively. The access to standard pellet diet purchased from the national office of animal feed, Bejaia (ONAB) and water *ad libitum* were allowed for animals. The experiments were carried out in accordance with the current guidelines for the care of laboratory animals, and the ethical guidelines for investigations of experimental pain in conscious animals, as specified by the National Research Council Academies[30]. The number of animals was the minimum necessary to demonstrate the consistent effects of the drug treatments.

Drugs and Reagents

The chemicals (acetic acid and formalin) used were purchased from Sigma Aldrich Gmbh (Steinheim, Germany). Paracetamol and normal saline water (0.9% NaCl) were used as the standard drugs and the control in all studies.

Phytochemical Screening

The phytochemical screening of the infusion extract of *M. deserti* De Noé was performed following the method of Harborne[31] and Siddiqui *et al.*[32]. Phytochemical constituents such as flavonoids, terpenoids, saponins, alkaloids, tannins, carotenoids, quinines, lipoid and steroids were qualitatively analyzed.

Acute Toxicity of *M. deserti* De Noé in Mice

The acute toxicity study of *M. deserti* De Noé infusion extract was assessed in mice of both sexes, as per OECD-423 guidelines (organization for economic co-operation and development)[33], with slight modifications. Mice were separated into six groups, each consisting of five males and five females mice (n=10). The infusion extract was administered with the doses of 5 g/kg, 7 g/kg, 9 g/kg, 11 g/kg and 13 g/kg bw The control group received normal saline water at a dose of 20 mL/kg bw Food and water were withheld 4 h after the drugs administration and the mice were closely observed for the 4 h and then once a day up to 14 days.

Antinociceptive Studies

Acetic Acid Induced Writhing Response in Mice

The analgesic activity was evaluated using acetic acid induced writhing method in mice following the

method of Sawadogo et al.[34] with slight modification[35-36]. The acetic acid was administered intraperitoneally to animals to create pain sensation. The animals were divided into five groups with six males in each (n=6), they were fasted for 19 h prior to experiments. The groups 1, 2 and 3 were treated with 250, 500 and 1000 mg/kg bw of the infusion extract; while the groups 4 and 5 received normal saline (control) and paracetamol (100 mg/kg bw) as a drug reference respectively. The extract and vehicle were administered orally 30 min before the intraperitoneal injection of the acetic acid (0.6%, v/v in normal saline, 10 mL/kg bw), and the animals were placed individually in transparent plastic cages for counting the number of writhing they made in 10 min beginning just 5 min after their administration. Contraction of the abdominal muscles accompanied by stretching the hind limbs was accepted as writhing movements[37]. A significant reduction in the number of writhing compared to the control animals was considered as an antinociceptic response[38]. The analgesic effect was calculated as the inhibition percentage of writhing.

$$\% \text{ inhibition} = (1 - Wt/Wc) \times 100$$

Where Wc is the average writhing response of the control group and Wt is the average writhing response of the treated group.

Formalin Induced Paw Licking in Mice

In this experiment, we used the method of Ullah et al.[38] with slight modifications[39], where pain was induced by formalin. The five groups of mice (n=6); vehicle control (normal saline water, 0.5 mL), paracetamol (100 mg/kg bw) and the infusion extracts of the plant (250, 500 and 1000 mg/kg bw), were administered orally thirty minutes after the subcutaneously injection of 50 μL of a freshly prepared 0.6% formalin solution that was injected under the plantar surface of the right hind paw of each mouse. The time in second spent in licking and biting responses of the injected paw was taken as an indicator of pain response. Antinociceptive effect was determined in two phases. The early phase was recorded during the first 5 min, while the late phase was recorded during the last 15 to 30 min. The inhibition percentage of the paw licks for both phases calculated by following formula:

$$\% \text{ inhibition} = \frac{Do\text{-}Dt}{Do} \times 100$$

Where Do is the average number of paw licks of the control group and Dt is the number of paw licks of the treated group.

Hot Plate Test in Mice

The 'hot-plate' test (thermal test) used in this study was described by Lanhers et al.[40] and Ojewole[41] to evaluate the analgesic activity. The temperature of the hot plate was regulated at 55°±0.5°C. The five groups of 6 mice each were fasted for 18 h and water was provided ad libitum. The mice of each group were placed on the hot plate in order to obtain its response to electrical heat induced pain stimulus. Licking of the paws or jumping out of the hot plate was taken as an indicator of pain response. Reaction time in seconds was taken as the interval between the instant that the animal reaches the hot plate till the moment that the animal licks its paws or jumps out. Each mouse was treated orally with control (normal saline water, 0.5 mL), paracetamol (100 mg/kg bw) or with the infusion extract at doses of 250, 500, 1000 mg/kg bw Thirty minutes after treatment, the reaction times of each group were evaluated five times individually each hour. The percentage thermal pain stimulus protection was calculated as the formula:

$$\% \text{ protection} = \frac{Ta \text{ - } Tb}{Ta} \times 100$$

Where Ta is the reaction time (s) after drug administration; Tb is the reaction time (s) before drug administration.

Antipyretic Activity in Rats

Antipyretic activity of M. deserti De Noé infusion extract was measured following the method described by Fadeyi et al.[42]. Pyrexia was induced in rats by subcutaneously injecting brewer's yeast suspension (20% w/v in normal saline, 10 mL/kg bw) into the rat's dorsum region. The initial rectal temperature of each rat was recorded 19 h before the yeast injection using a thermometer (Hartmann, Germany). The animals were then fasted for all the duration of the experiment, water was available ad libitum. Nineteen hours after the injection, the rectal temperature of each rat was recorded again to determine the pyretic response to yeast. Only rats that showed an increase in temperature of at least 0.5°C were selected and then rats were divided into five groups with six each (n=6). The infusion extract at doses of 250, 500 and 1000 mg/kg bw of M. deserti De Noé were administered orally, while the control group was given normal saline water and the fifth group was treated with paracetamol (100 mg/kg bw). The temperature was measured at 1, 2, 3 and 4 h after drug and vehicle administrations.

Statistical Analysis

Results are expressed as mean ± standard deviation (S.D.). Statistical significance was determined using one way ANOVA followed by Tukey's test for multiple comparisons. *p*-values<*0.05* were considered as significant.

Results

Phytochemical Screening

Phytochemical screening of the infusion extract of *M. deserti* De Noé revealed the presence of various bioactive components of which condensed tannins, catechic tannins, alkaloid, steroids, saponins and terpenoid (Table 1). In addition, we demonstrated the presence of high content of total phenolic compounds such as flavonoid, coumarine and glucosides.

Acute Toxicity

Oral administration of *M. deserti*'s infusion extract (up to 13 g/kg bw) did not show any signs of toxicity or behavioral changes in mice during the initial 4 hours after *M. deserti* De Noé infusion extracts

Table 1 — Phytochemical Analysis of the Infusion Extract of *M. deserti* De Noé Aerial Parts

Extract	Phytochemical constituents	Results
	Flavonoids	+ +
M. deserti's infusion extract	Lipoids	-
	Condensed tannins	+ + +
	Catechic tannins	+ +
	Alkaloids	+ + +
	Steroids	+
	Saponins	+ + +
	Quinines	-
	Terpenoids	+
	Coumarine	+ + +
	Glucosides	+ + +

Symbols
'+++' indicates presence in high concentration;
'++' indicates presence in moderate concentration;
'+' indicates presence in low concentration and
'-' indicates absence of phytochemicals.

Table 2 — Effect of the Infusion Extract of *M. deserti* De Noé on Acetic Acid-induced Writhing in Mice

Groups	Dose	Number of writhing	% Inhibition
Control		57±1.7	-
Paracetamol	100 mg/kg	29±1.4[***]	49.12
Infusion extract of	250 mg/kg	41±2.2[***£]	28.07
M. deserti De Noé	500 mg/kg	33±2.09[***£]	42.10
	1000 mg/kg	29±1.7[***£]	49.12

Data represent mean±SD, (n=6). (-): no activity, [***]p<0.001 significant from the control, [£]p<0.05 significant from the reference drug (Paracetamol) (one way ANOVA followed by Tukey's test).

administration. During the 14 days of experiment, no deaths were observed in any of groups.

Acetic Acid Induced Writhing Response in Mice

The results of the analgesic effects of *M. deserti* De Noé infusion extracts on acetic acid induced writhing test in mice are presented in Table 2. The oral administration of the infusion extract significantly (*p<0.001*) decreased in a dose-dependent manner the number of writhing induced by acetic acid. The infusion extract at doses of 250 and 500 mg/kg b.w. showed 28.07% and 42.10% inhibition of writhing respectively compared to the control group, whereas at higher dose (1000 mg/kg b.w.) significantly (*p<0.001*) was found to be the same as the standard drug (Paracetamol, 100 mg/kg bw) with 49.12% inhibition.

Formalin Induced Paw Licking

The effect of *M. deserti*'s infusion extract on formalin induced paw licking in mice is shown in Fig. 1 and Fig. 2. There was a dose-dependent
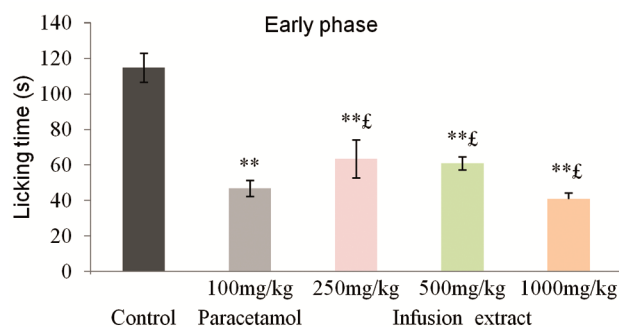

Fig. 1 — Analgesic activity of the infusion extract of *M. deserti* De Noé aerial parts using formalin induced paw licking test on the early phase *Data represent mean±SD, (n=6),* [**]*p<0.01 significant compared to control,* [£]*p<0.05 significant compared to reference (one way ANOVA followed by Tukey's test)*
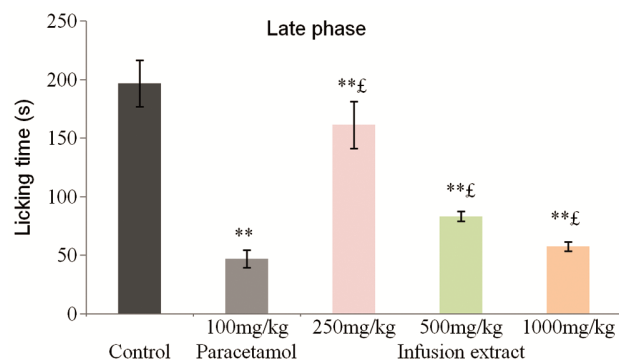

Fig. 2 — Analgesic activity of the infusion extract of *M. deserti* aerial parts using formalin induced paw licking method on late phase *Data represent mean±SD, (n=6),* [**]*p<0.01 significant compared to control,* [£]*p<0.05 significant compared to reference (one way ANOVA followed by Tukey's test)*

Table 3 — Analgesic Activity of the Infusion Extract of *M. deserti* De Noé Using the Hot Plate Method

Groups	Dose	Reaction time at different time intervals (in s)					
		0 h	30 min	1h	2 h	3 h	4 h
Control		9.263±1.03	7.555±0.5	4.856±0.8	5.431±1.03	3.533±0.5	3.933±0.5
Paracetamol	100 mg/kg	7.843±0.9[*]	16.028±1.7[**]	17.635±1.2[**]	20.445±1.3[*]	19.958±0.7[**]	20.063±0.6[**]
Infusion	250 mg/kg	8.425±0.3[*]	14.513±0.7[**]	11.44±1.2[**£]	10.616±1.1[**£]	9.12±0.8[**£]	8.706±0.6[**£]
extract of *M.*	500 mg/kg	9.168±0.9[*]	14.601±1.04[**]	12.62±0.8[**£]	14.686±0.8[**£]	13.16±0.7[**£]	10.293±0.3[**£]
deserti De Noé	1000 mg/kg	7.965±1.2[*]	9.355±0.7[**£]	18.216±0.6[**]	16.853±0.5[**£]	19.063±1.6[**]	18.261±1.07[**]

Values represent mean±SD, (n=6), [*]*p<0.05*[**]*p<0.01 significant compared to control,* [£]*p<0.05 significant compared to paracetamol (one way ANOVA followed by Tukey's test).*

Table 4 — Effect of *M. deserti*'s Infusion Extract Aerial Parts on Yeast Induced Pyrexia in Rats

Groups	Dose	Before yeast	After yeast	Time after treatment (h)			
		0 h	19 h	1 h	2 h	3 h	4 h
Control		36.93±0.1	38.08±0.1	38.16±0.3	38.23±0.3	38.46±0.2	38.61±0.3
Paracetamol	100 mg/kg	37.48±0.3	38.46±0.3	37.58±0.3[*]	37.1±0.4[**]	37.31±0.3[**]	36.98±0.3[**]
Infusion extract of *M.*	250 mg/kg	37.1±0.1	38.66±0.2	37.55±0.3[*]	37.33±0.5[**]	36.93±0.6[**]	36.68±0.5[**]
deserti De Noé	500 mg/kg	36.6±0.3	38.2±0.2	37.93±0.3[*]	37.55±0.4[**]	36.96±0.5[**]	36.85±0.3[**]
	1000 mg/kg	36.68±0.3	38.33±0.2	38.05±0.4[*]	38.1±0.4[**£]	37.46±0.3[**]	37.48±0.4[**]

Values represent mean±SD, (n=6).[*]*p<0.05,* [**]*p<0.001 significant compared to control,* [£]*p<0.05 significant compared to paracetamol (one way ANOVA followed by Tukey's test).*

inhibitionof both phases in the extract tested of the formalin test. The infusion extract at the doses of 500 and 1000 mg/kg bw significantly (*p<0.001*) inhibited the liking response in both the early phase (46.91%, and 64.39% respectively), and the late phase (57.69% and 70.75% respectively) of the formalin test, while at the dose of 250 mg/kg bw, the infusion extract exerted its action only on the early phase (44.75%) compared with the late phase (17.98%). The standard drug paracetamol (100 mg/kg bw) showed a significant (*p<0.001*) inhibition in both phases, with 59.15% inhibition in the early phase and 76.09% inhibition in late phase.

Hot Plate Test

The results of the effect of *M. deserti* De Noé infusion extract on hot plate induced pain in mice are presented in Table 3 and Fig. 3. The infusion extract produced a dose-related significant (*p<0.01*) analgesic effect that continued for 4 h (58.21%) at the dose of 1000 mg/kg b.w. and until 3 h (37.57%) at the dose of 500 mg/kg bw, but at the low dose of 250 mg/kg bw this extract presented a short analgesic activity (41.94%) against thermal pain stimulus that continued only 30 min after the administration. The paracetamol at the dose of 100 mg/kg bw increased the reaction time of heat sensation in mice with 61.63% protection in the 3rd hour which was significantly greater (*p<0.01*) than that seen with the control group.
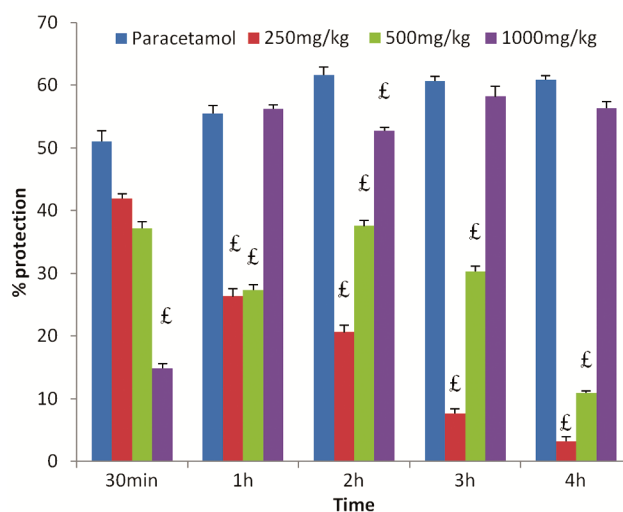

Fig. 3 — Protection percentage against thermal pain stimulus of *M. deserti* De Noé infusion extract at different time intervals on hot plate test [£]*p<0.05 significant compared to paracetamol (one way ANOVA followed by Tukey's test)*

Antipyretic Activity in Rats

The effect of *M. deserti* De Noé infusion extracts on yeast induced pyrexia is shown in Table 4. Subcutaneous injection of yeast suspension clearly increased rectal temperature of rats 19 h after yeast injection. The oral administration of the infusion extract of *M. deserti* De Noé at the dose of 250 mg/kg and 500 mg/kg bw after 3 h of treatment caused a significant (*p<0.01*) decrease in temperature compared to control group. In contrast, the higher

dose (1000 mg/kg bw) did not elicit a greater reduction from yeast induced pyrexia as would have been expected. However, the infusion extract at the dose of 250 mg/kg bw showed the highest activity even more than the reference drug (Paracetamol, 100 mg/kg bw).

Discussion

In this study, antinociceptive and antipyretic activities of the infusion extract of *M. deserti* De Noé aerial parts were evaluated in addition to the determination of its acute toxicity profile. The antinociceptive potential was assessed using the chemicals (acetic acid and formalin) and the thermal stimuli models (hot plate test) in mice, while the antipyretic test was evaluated on yeast induced pyrexia in rats. The obtained results showed that the infusion extract of this plant demonstrate high significant ($p<0.001$) effects in all the models used while the acute toxicity results indicate that the *M. deserti*'s infusion extract is harmless for the medicinal use as the relatively high LD_{50} value (>13 g/kg) from a single exposure, probably suggests that this plant is safe.

In an attempt to determine whether the infusion extract attenuated either the peripheral or central, or both levels of nociception, acetic acid induced writhing, formalin induced paw licking and thermal induced nociceptive tests were performed.

Acetic acid, the peripheral analgesic agent, causes inflammatory pain by inducing abdominal constrictions and stretching of hind limbs[43]. Recently, it has been found that this response is mediated by the prostaglandin pathways[44]. Therefore, the agent reducing the number of writhing will provide analgesic effect preferably by inhibition of prostaglandin synthesis, a peripheral mechanism of pain inhibition[45]. Our results showed that the infusion extract of *M. deserti* De Noé in dose-dependent manner caused high significant ($p<0.001$) reduction in the number of writhes. The ability of the infusion extract of *M. deserti* De Noé aerial parts to attenuate the acetic acid induced writhing response test indicates the presence of analgesic compounds that might influence the prostaglandin pathways.

The formalin test is a model of continuing pain including peripheral inflammation and central sensitization. The injection of formalin into the mouse hind paw initiates triphasic spontaneous nociceptive behaviors consisting of flinching, licking and/or biting

of the injected paw[2]. This method shows a biphasic response, the early phase, classified as a neurogenic pain, is an acute response observed immediately after the administration of formalin and lasts for 5 min (0–5 min) as a result of an immediate action of injected formalin on nociceptors. The late phase, classified as an inflammatory pain, is a tonic response resulting from the inflammatory processes generated by the release of inflammatory mediators such as histamine, serotonin, prostaglandin and bradykinin[46] and the activation of the neurons in the dorsal horns of the spinal cord which appears between 15 and 60 min after the formalin administration[47-48]. The results of the present study showed that the infusion extract of *M. deserti* De Noé produced antinociceptive activity against both neurogenic and inflammatory phases of formalin induction which suggests that it contain active analgesic principles acting centrally and peripherally, where the last action is supported by the results recorded in the acetic acid induced writhing test.

Another model of nociception that has been widely used to further support the antinociceptive effect observed in any new compound or extract is the thermal induced nociceptive model or hot plate test. The hot plate test measures the response to a brief, noxious stimulus having a close resemblance to clinical pain. This test measures the complex responses to a non-inflammatory, acute nociceptive impulse and is one of the selective models for studying only the central antinociceptive activity[49]. Drugs that act centrally activate the release of endogenous peptides, which is then carried to the spinal cord to inhibit the pain impulse transmission within the dorsal horn[50]. Based on the ability of the infusion extract to prolong the latency on hot plate, we suggest that this extract possessed centrally mediated antinociceptive activity against the thermal induced nociception.

To investigate the antipyretic effect of *M. deserti*'s infusion extract, the yeast induced pyrexia test in rat was carried out. Antipyretic activity is a characteristic of drugs or compounds which have an inhibitory effect on prostaglandin biosynthesis[51]. It is well known that pyretic activity involves stimulation of the region in the hypothalamus that controls body temperature; via prostanglandins synthesized within the central nervous system and that the blood-brain barrier prevents drug molecules or other chemicals from entering the central nervous system[44]. Regulation of body temperature

requires a delicate balance between production and loss of heat, and the hypothalamus regulates the set point at which body temperature is maintained[52]. The infusion extract of *M. deserti* De Noé aerial parts possesses a significant antipyretic effect in yeast-induced temperature in rats. So, we suggest that this extract may exhibit central action because pyrexia is central processes[42].

Furthermore, the chemical screening for compounds known for their potential activities was investigated. Phytochemical screening of the infusion extract of *M. deserti* De Noé aerial parts indicates the presence of tannins, alkaloids, steroids, terpenoids and a high amount of phenolic compounds. Flavonoids constitute a wide array of biologically active compounds that are found abundantly in plant kingdom and dietary intake. They are reported to be effective against different diseases such as antioxidant, analgesic, anti-inflammatory[53-55], antimicrobial[56], hepatoprotective[57] and anticancer[25] activities. Furthermore, condensed tannins have been suggested to possess free radical scavenging and antioxidant, anti-inflammatory, and hepatoprotective activities[58]. Besides, alkaloids are well known for their abilities to inhibit pain perception[1]. Based on these reports, it is possible that the antinociceptive and antipyretic activities of the infusion extract of *M. deserti* De Noé may be due to the presence and the action of flavonoids, tannins, alkaloids or terpenoids.

Conclusion

To the best of our knowledge, this work reveals, for the first time, that *Marrubium deserti* De Noé infusion extract possesses antinociceptive and antipyretic effects, suggesting that the mechanism of action seems to be similar to NSAIDs drugs such as paracetamol. It has been proved that *M. deserti* De Noé has obvious beneficial effects against centrally and peripherally pain models. The relatively high LD_{50} value (>13 g/kg bw) obtained for the plant shows that it is safe. These findings justify the use of this plant in the Algerian traditional medicine in the treatment of various types of inflammations and pains. However, the chemical constituents responsible for the pharmacological activities remain to be investigated.

Acknowledgement

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