



Original Article

Analgesic and anti-inflammatory activities of hydro-alcoholic extract of *Lavandula officinalis* in mice: possible involvement of the cyclooxygenase type 1 and 2 enzymes



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ABSTRACT

Lavandula officinalis Chaix, Lamiaceae, extracts can inhibit inflammation and also pain induced by formalin in mice. This study evaluated the effects of *L. officinalis* hydro-alcoholic extract on pain induced by formalin and also cyclooxygenase (COX) type 1 and 2 activity in mice. To evaluate probable analgesic and anti-inflammatory effects of the extract, flowers were prepared by maceration and extraction in alcohol and their analgesic effects were studied in male mice, using formalin and hot plate tests. The effect of intraperitoneal hydro-alcoholic extracts of *L. officinalis* (100, 200, 250, 300, 400 and 800 mg/kg), subcutaneous morphine (10 mg/kg), dexamethasone (10 mg/kg; *i.p.*) and indomethacin (10 mg/kg; *i.p.*) on formalin induced pain were studied. Our results indicated that administration of the extract (100, 200, 250, 300, 400 and 800 mg/kg; *i.p.*) has inhibitory effects on inflammation induced by formalin injection into the animals hind paw. Moreover, this inhibitory effect was equal to the effects of morphine, dexamethasone and indomethacin. The extract in 100, 200 and 300 mg/kg; significantly reduced heat-induced pain. The extract also reduced COX activity in dose dependent manner, where the inhibitory effect on COX1 activity was 33% and on COX2 activity was 45%. Here for the first time we show that *L. officinalis* extract can modulate pain and inflammation induced by formalin by inhibition of COX enzymes.

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Introduction

Natural products are believed to be an important source of new chemical substances with potential therapeutic application. Several plant species were traditionally used as analgesics. In general, the herbal plant usage in treatment of disease and pain relief is one of the important strategies in medicine. *Lavandula officinalis* Chaix, Lamiaceae, commonly known as “Ostokhodous”, is indigenous to the Arabic, Mediterranean Coasts and Asia Minor (Ghelardini et al., 1999; Akhondzadeh et al., 2003). This plant, from the mint family, has small subdued green leaves, is 30–50 cm height with small purple flowers and has a rather pungent taste. *L. officinalis* is used in traditional and herbal medicine for the

treatment of several gastrointestinal, nervous and rheumatic disorders (Leung and Foster, 1996). The chemical composition and pharmacological evaluation of *L. officinalis* has been the subject of several studies over the years. Most of these studies were focused on the extracts, fractions, and essential oils of the aerial parts and flowers of the plant. In pharmacological and biological tests, extracts, fractions, and essential oils of *L. officinalis* are reported to have antispasm and soporific, antitension, antioxidant, CNS-depressant, anticonvulsive, sedative, local anesthetic, antibacterial, and mast cell degranulation inhibitory effects (Ghelardini et al., 1999; Hohmann et al., 1999; Kim and Cho, 1999; Lis-Balchin and Hart, 1999; Shahriary et al., 2005). It is well accepted that *L. officinalis* extract contains linalool, acetate linalool, monotril, cezoiterpen, luteolin, ursolic acid, coumarin, and umbelliferone (Kakkalou, 1988; Hajhashemi and Ghannadi, 2003; Barocelli et al., 2004). Hajhashemi and Ghannadi (2003) showed that the aquatic, alcoholic, and phenolic extracts of this plant have anti-nociception

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effects in the second phase of formalin test, but only the phenolic and alcoholic extracts had been able to prevent the first phase of the formalin test. Also application of this plant could not prevent the edema evoked by carrageenin administration (Hajhashemi and Ghannadi, 2003). It was proved that inhaling the leaves of the *Lavandula officinalis* could attenuate pain evoked by hotplate test, and stomach graze induced by high dose administration of ethanol and ascorbic acid (Barocelli et al., 2004). Therefore, it seems that the components of *L. officinalis* have an important role in the reduction of the inflammatory pain. COX enzyme, responsible for the production of prostaglandins, is the key enzyme in causing inflammatory pain. Over-activity of COX in inflammation can produce peripheral sensitization of primary afferent. Three types of COX (1, 2 and 3) had been identified. Studies have shown that only types 1 and 2 had roles in inflammatory pain (Simmons et al., 2004). Non-steroid anti-inflammatory drugs such as indomethacin could induce their anti-inflammatory and analgesic effects by blocking the action of such enzymes (Payan, 1992). The purpose of the present study was to evaluate the analgesic and anti-inflammatory effect of the hydro-alcoholic extract of *L. officinalis* in mice using formalin and hot plate tests. In addition, the inhibitory effects of the extract on COX 1 and 2 activity was measured *in vitro*.

Materials and methods

Animals

Male NMRI mice with mean weight of 25–30 g were purchased from Pasteur Institute (Tehran, Iran). The animals were exposed to 12 h of daylight and were fed standard rat food and tap water (environment temperature, $23 \pm 2^\circ\text{C}$). In each group, six mice were studied. This study was conducted according to the standard ethical guidelines and approved by the local ethical committee (The Baqiyatallah (a.s.) University of Medical Sciences Committee on the Use and Care of Animals, 87/381, July 25, 2009). The experiments were done in the light period (10 am–4 pm).

Preparation of plant extract

Dried flowers and head branches of *Lavandula officinalis* Chaix, Lamiaceae, were harvested in summer 2012 from the botanical farm of the Faculty of Medicine of Baqiyatallah (a.s.) University. The flowers were sent to the laboratory of Pharmaceutical College of Shahid Beheshti Medical University, assessed by M. Kamalinejad, and given the voucher number code of 408. Plant flowers and head branches were powdered and the extract was prepared using 100 g of the powder and 100% ethylic alcohol by maceration. The extract was separated and filtered by Whatman filter papers. The prepared extract was concentrated by vacuum evaporation and then was dried in low temperatures. The extract was kept in a capped bottle at 4°C in a refrigerator for future use.

Estimation of plant extracts effective dose 50%

For this propose, the effect of different doses of the extract on formalin-induced pain were evaluated and the dose-response curve was drawn. The R^2 was calculated for the curve and was chosen as $\text{ED}_{50}\%$. The doses used in this study are according to the $\text{ED}_{50}\%$ which was 185 mg/kg. The doses of the extract were chosen as $\text{ED} \pm 2 \text{ SD}$ and then were corrected.

Formalin test

Formalin test was done according to the modified method of Dubuisson and Dennis, (1977). Each animal was placed inside a Plexiglas box with the dimensions of $30 \text{ cm} \times 30 \text{ cm} \times 30 \text{ cm}$

(Length \times width \times height) after injection of formalin in plantar part of right foot. The position of the foot and the way animals responded to formalin (20 μl ; 2%) injection were evaluated by observers and scored on a scale of 0–3 depending on the condition of the animal's foot. No pain and normal movement of the animal was scored zero. If the animal put its foot on the floor of the box but avoided putting its body weight on the injected foot (claudicating), it was scored 1. Score 2 was given to the animals that avoided putting their injected foot on the floor of box. Score 3 was documented when the rat bit or licked the injected foot, which was taken to be an indication pain. Each animal was injected with one of these drugs 30 min before the injection of formalin: *Lavandula* hydro-alcoholic extract, morphine, dexamethasone and indomethacin.

Determining the degree of inflammation

For determining the degree of inflammation induced by formalin (Ferreidoni et al., 2000; Ahmadiani et al., 2000), each animal's left foot was considered as the control foot, in which saline was injected. Animal's right and left feet were separately placed in a container that contained mercury and the exact weight of the foot was determined as follows. By calculating the weight change of mercury due to immersion of the left foot (control) and the right foot (test), foot weight changes were determined after formalin injection. This weight change was deduced from the volume change through dividing it by 13.6 (density of mercury). The anti-inflammatory effect of the chemicals was assessed in 5, 10, 20, 25 and 30 min intervals.

Assay of the effects of *L. officinalis* extract on COX activity

As mentioned in the previous section, interstitial fluid from the formalin-injected paw was collected using a fine needle (gauge 30) and was added to the ELISA kit which was poured in three wells by COX type 1 or 2 enzymes. After 30 min of incubation at 37°C , the enzyme product was measured by an ELISA reader at 870 nm.

Hot-plate test

The hot-plate test was performed according to the method described by King et al. (2001). The animals were placed individually on a hot plate (Pars AZMA Co., Isfahan, Iran), maintained at $46 \pm 1^\circ\text{C}$ and the time between the placement of the animal on the hot plate and the occurrence of either the licking of the hind paws, shaking or jumping off from the surface was recorded as the response latency. A cut-off time of 30 s was considered if the animal did not show any reaction to the painful stimulus.

Chemicals

The following drugs were used in this study: Morphine sulfate (Temad Co., Tehran, Iran), indomethacin hydrochloride (Sigma, USA) and dexamethasone (Sina Darou, Iran). Drugs were dissolved in saline and injected intraperitoneally to the animals in volumes of 10 ml/kg except for morphine which was given subcutaneously. The extract of *L. officinalis* was dissolved in physiologic saline and then injected intraperitoneally. In this study, morphine was used as a standard analgesic drug, indomethacin as a non-steroid anti-inflammatory drug and dexamethasone, as an anti-inflammatory drug were used to provide positive witnesses to compare the anti-inflammatory and analgesic function of the extract.

Experimental design

Experimental animals received subcutaneous morphine (10 mg/kg), or dexamethasone (10 mg/kg; *i.p.*), indomethacin

(10 mg/kg; *i.p.*), saline (10 ml/kg), or different doses of *L. officinalis* extract (100, 200, 250, 300, 400 and 800 mg/kg) intraperitoneally 30 min before formalin was injected. Animals' responses to formalin-induced pain and inflammation were evaluated after formalin was injected into the plantar portion of the right paw. Hot plate evoked pain was also evaluated. Animals' serum was collected 30 min after formalin was injected into the plantar part of the right foot and the effects of the chemicals on enzyme inhibition were studied.

Statistical analysis

All data were expressed as mean \pm SEM. The statistical significance was determined using a One-way Analysis of Variance (ANOVA), followed by Tukey *post hoc* test. $p < 0.05$ was considered as an indication of a significant difference.

Results

Effect of *L. officinalis* extract on pain responses in formalin test

First, 20 μ l of 2% formalin was injected in to the right hind paw. Then, the pain response evoked by formalin was determined. As expected, a two-phase response was seen after the administration of formalin: (1) a first phase (phase neurogenic) lasted up to 5 min following formalin injection and (2) a secondary phase (inflammatory phase) lasted 20–25 min (data not shown). These two phases actually reflect the acute and chronic phases of formalin administration respectively. According to these results, the first 5 min was considered as the peak of acute phase and the 20th to 25th min as the peak of the chronic phase. The inhibitory effect of the extract on the chronic phase of the pain evoked by formalin was higher than morphine as an analgesic drug. However, the extract could not attenuate the acute phase (Fig. 1A). Therefore, these data

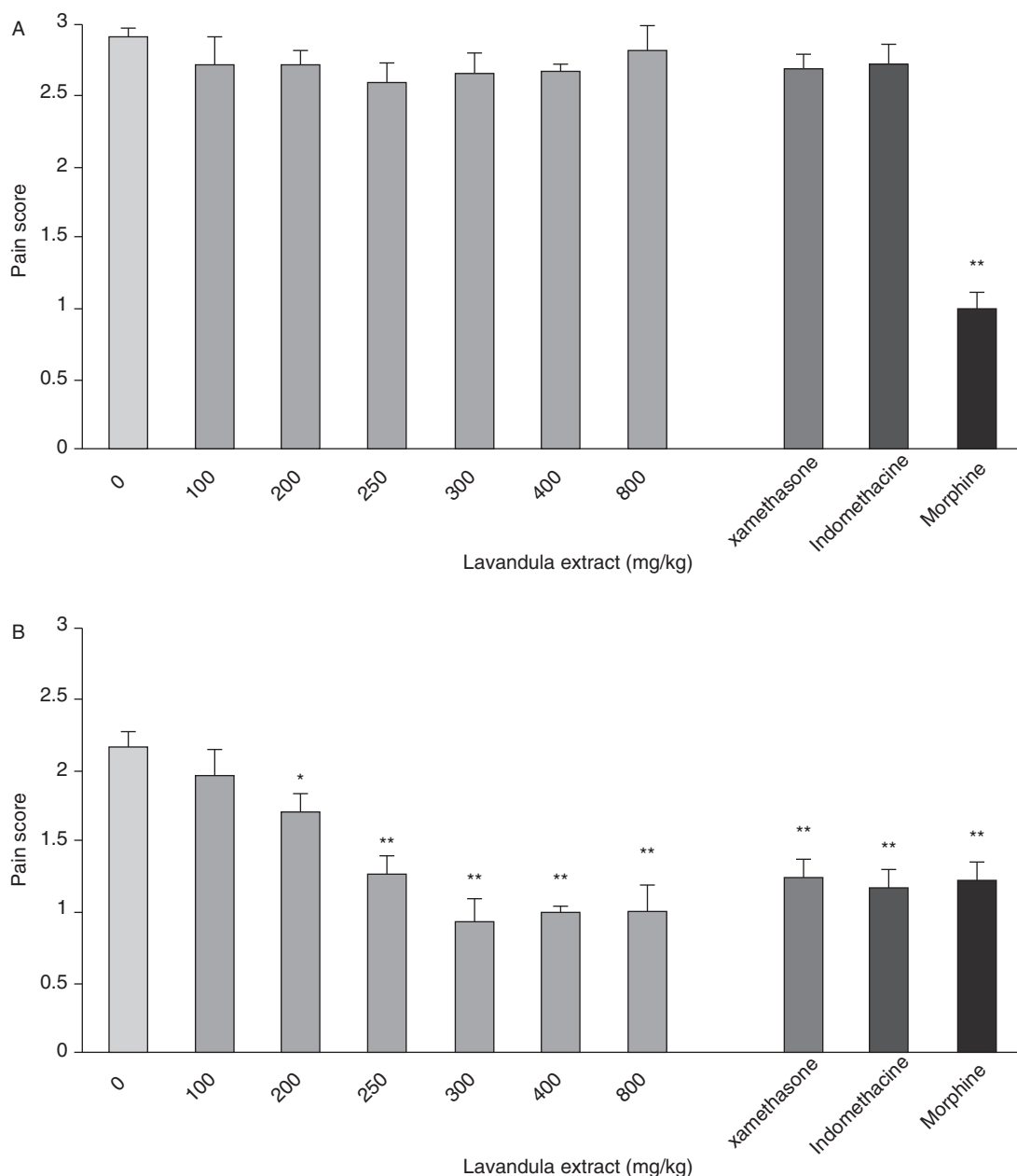


Fig. 1. (A) Effects of *Lavandula officinalis* extract on the acute phase of formalin test in mice. The extract cannot inhibit acute phase of the formalin test. Data showed as mean \pm SEM, for 6 mice, * $p < 0.05$, ** $p < 0.01$ different from experimental groups. (B) Effects of *Lavandula officinalis* extract on the chronic phase of formalin test in mice. The extract significantly inhibit chronic phase of the formalin test. Data showed as mean \pm SEM, for 6 mice, * $p < 0.05$, ** $p < 0.01$ different from experimental groups.

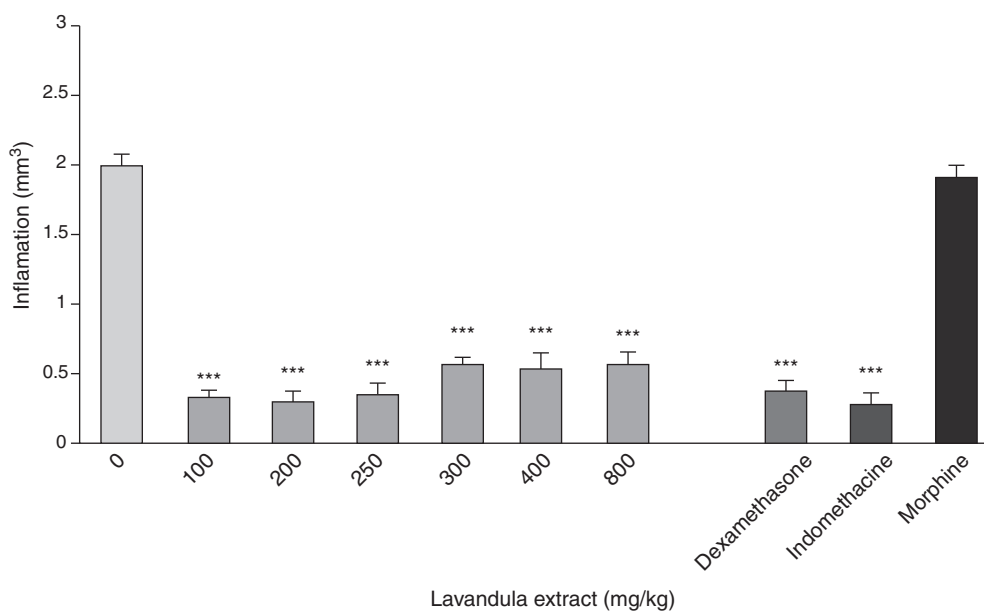


Fig. 2. Effect of *Lavandula officinalis* extract on inflammation induced by formalin in mice. The inflammation was reduced by the extract, dexamethasone, and indomethacin but not morphine. Data showed as mean \pm SEM, for 6 mice, *** $p < 0.001$ different from Saline group.

suggest that the extract had a critical role in the second phase of the pain in formalin test (Fig. 1B).

Effect of *L. officinalis* extract on inflamed hind paw

The results showed that the administration of the extract (100, 200, 250, 300, 400 and 800 mg/kg, *i.p.*) has inhibitory effects on the inflammation induced by formalin injection into the animals hind paw. This inhibitory effect was comparable to the effects of indomethacin and dexamethasone. The anti-inflammatory effects of the extract were much stronger than morphine (Fig. 2). The results showed that the maximum inflammation in hind paw was observed 25–30 min after the administration of formalin.

Effect of *L. officinalis* extract on COX1 and COX2 activity

The effect of the extract on COX1 and COX2 activity is shown in Fig. 3A and B. The extract attenuated COX activity. However, its inhibitory effect for COX1 activity was 33% and for COX2 was 45%. The magnitude of inhibitory effect of the extract was higher than indomethacin and dexamethasone (Fig. 3A and B).

Effect of *L. officinalis* extract on pain responses in hot plate test

The mean latency time of pain responses to thermal stimuli in hot plate test is shown in Fig. 4. Both the extract (100, 200 and 300 mg/kg; *i.p.*) and morphine significantly exerted protective effects on heat-induced pain in mice. However, morphine (10 mg/kg, *s.c.*) markedly increased pain latency time. Moreover, high doses of the extract (400 and 800 mg/kg; *i.p.*) did not show significantly different effects (Fig. 4).

Discussion

In the current study, we demonstrate that intraperitoneal treatment with hydro-alcoholic extract of *L. officinalis* produces significant analgesic and anti-inflammatory activity in the chronic phase of formalin test and also hot plate test in mice. Moreover, these results suggest that hydro-alcoholic extract of *L. officinalis*

could modulate pain by means of COX2 over-activity. Furthermore, various doses of the extract had no effect on the acute phase of formalin test. The antinociception effect of the extract on the chronic phase of the pain induced by formalin was comparable with dexamethasone and indomethacin. Previous studies have been shown that dexamethasone, as a corticosteroid drug, could inhibit the chronic phase of the formalin induced-pain by means of inhibiting the phospholipase A2 activity (Hunnskaar and Hole, 1987). Simmons et al. (2004) have shown that indomethacin blocked the chronic phase of the formalin-evoked pain by means of inhibition of COX activity. In the present study, it is demonstrated that anti-nociception effect of the extract, similar to indomethacin, is modulated by COX activity. Therefore, it seems that the extract decreased production of prostaglandins, leading to pain and inflammation relief (Payan, 1992). Therefore, it seems that indomethacin, dexamethasone and the extract share a common mechanism on formalin evoked pain. One important finding in this study was the inhibitory effect of the extract on COX2 activity. However, COX1 activity was decreased by the administration of 300 and 400 mg/kg of the extract. It is highly likely that COX-1 is constitutively expressed, while COX-2 is inducible and produces prostanoids that involved in the inflammation (Fukutake et al., 2000). Consequently, these results indicate that the mechanism of analgesic and anti-inflammatory effects of the extract are modulated by COX2 activity. It is well accepted that COX2 could be inhibited by non-steroid anti-inflammatory drugs such as indomethacin and aspirin (Simmons et al., 2004). Moreover, several studies reported that dexamethasone has anti-inflammatory effects in various animals (Simmons et al., 2004). Hajihashemi et al. (2003) have also shown that the extract of *L. officinalis* leaves could inhibit the formalin induced-chronic pain, abdomen writhing and carrageenan evoked edema. Likewise, the administration of the high doses of the essential oils and polyphenolic fraction of *L. officinalis* blocked acetic acid evoked pain (Barocelli et al., 2004). In the present study, the extract also decreased formalin evoked-edema and added to the concept that the aquatic-alcoholic extract of *L. officinalis* has analgesic effects. Surprisingly, our data revealed that extract significantly increased analgesia duration in low doses of extract (100, 200 and 300 mg/kg), whereas this effect was not significant in high doses (400 and 800 mg/kg). In other words, this increasing effect of extract was

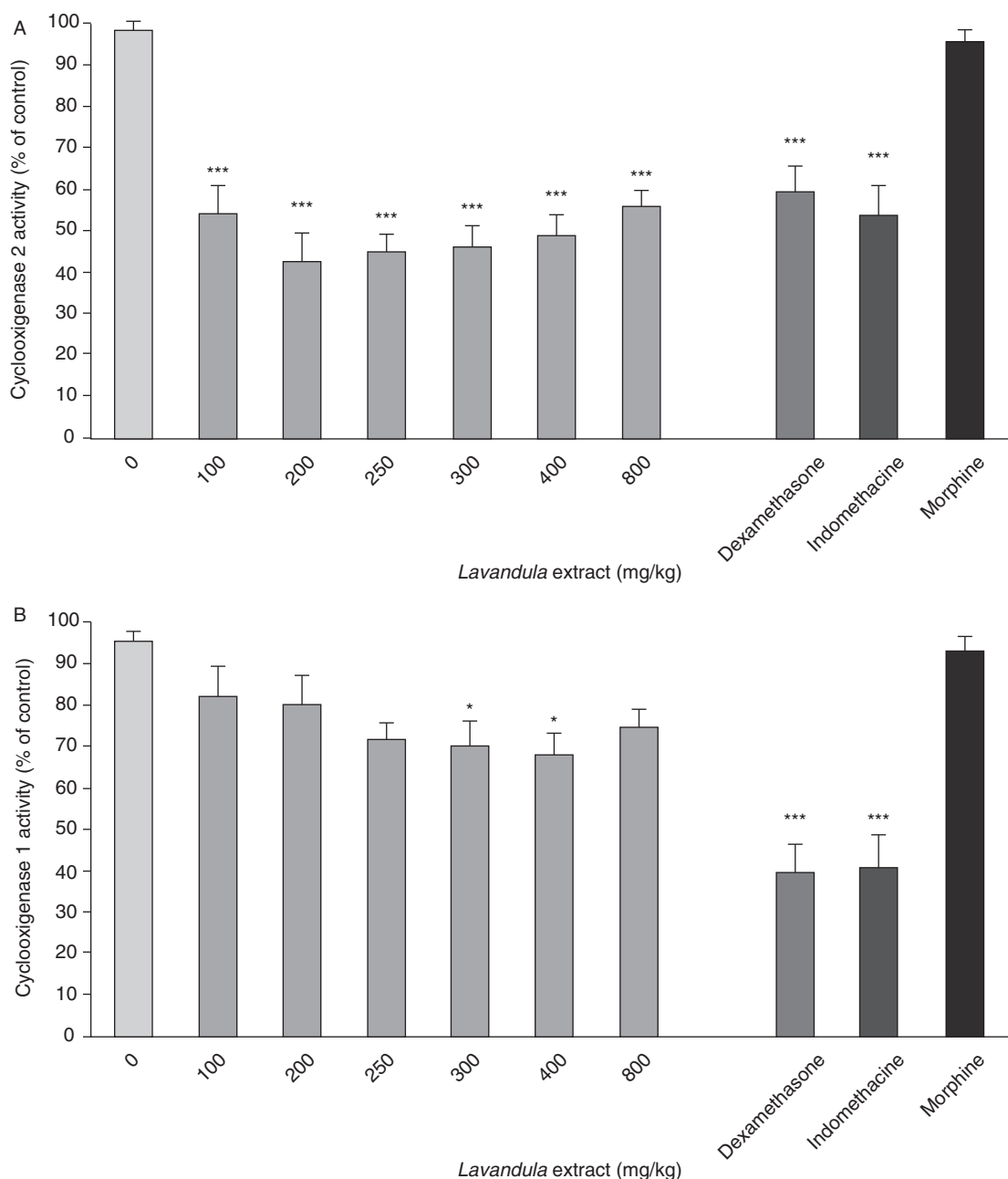


Fig. 3. (A) Inhibition of the enzyme COX 2 by the extract of *Lavandula officinalis*. The effect is comparable with the effect of dexamethasone and indomethacin. Data showed as mean \pm SEM, for 3 \times 3 well, * p < 0.05 and *** p < 0.001 different from control group. (B) Inhibition of the enzyme COX 1 by the extract of *Lavandula officinalis*. Data showed as mean \pm SEM, for 3 \times 3 well, * p < 0.05 and *** p < 0.001 different from control group.

dose dependent. However, the inhibitory effects of the extract on pain score, inflammation, and also COX2 activity either increased with increase of dosage of the extract. It is suggested that different doses of extract may exert different influences on the pain system. It is necessary to be noted that the analgesic duration may not always change in parallel with the other inflammation parameters, indicating that different mechanisms might be involved in the duration of analgesia. Furthermore, the main finding of our study was the inhibitory effect of the extract on formalin-induced edematous in hind paw and also the effect of the extract on COX activity was dose-dependent. Therefore, it seems that one possible mechanism by which *L. officinalis* extract leads to pain and inflammation relief is COX system inhibition. It is necessary to mention that in this study the fractions of the extract were not separated, so these results could not explain which type of fraction had inhibitory

effect on COX activity. As to the identity the fractions of the extract responsible for inhibitory effect on COX activity, more studies will be necessary to help clarify this issue. Finally, the effect of *Lavandula* extract administration on pain induced by hot plate test was assessed. King et al. (2001) showed that the extract could prevent the pain resulting from hot-plate test at least in two doses. It is not clear which parts of upper spinal cord were active or suppressed by the extract to reduce the pain resulting from the hot-plate. However, Silva Brum et al. have shown that linalool increases GABAergic tonus and decreases glutamate content in mice brains (2001). Since it is well established that nearly 60% of the extract component is linalool (Hajhashemi and Ghannadi, 2003), and linalool has a major analgesic effect in case of the hot-plate test, although this has not been experimentally assessed. Barocelli et al. (2004) reported that the administration of *L. officinalis* leaves blocked pain

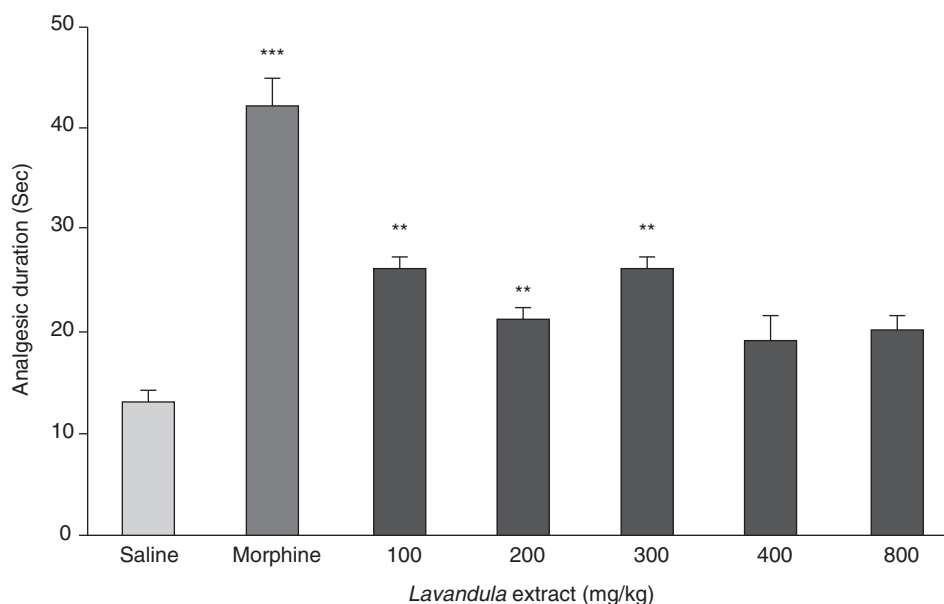


Fig. 4. The effect of *Lavandula officinalis* extract on the pain induced by hotplate test. The effect of morphine was much more than the effect of the extract. The results were shown by (mean \pm SEM) the time of pain in 6 animals. *** $p < 0.001$ and ** $p < 0.01$ were the difference from the control group.

in hot-plate tests. Administration of the essential oil with naloxone, atropine and mecamilamin could eliminate the analgesic effect of the extract, which indicates that the analgesic activity of the extract is dependent on cholinergic and opioidergic systems (Hajhashemi and Ghannadi, 2003). According to our results, it seems that the hydro-alcoholic extract of *L. officinalis* could block the chronic pain and the inflammation induced by formalin in mice by inhibiting COX1 and COX2 activity. Furthermore, the intraperitoneal administration of this extract inhibited pain in the hot-plate test.

Conclusion

Our results confirm and extend previous findings showing that *L. officinalis* extract, alleviates both pain, in the hot-plate test, and the chronic phase of formalin induced pain. We have also shown that the extract has anti-inflammatory effects. In addition, we have demonstrated that the analgesic and anti-inflammatory activity of *L. officinalis* depends on the inhibition of COX system.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Author's contribution

YH participated in all experiments; HS and GHM supervised the project and participated in all experiments; MD, AM, BH, HZ contributed to conception and design study; MR, SBH, HA, carried out the extraction; MB, AM, ZB, HG, analysis and interpretation of data with CJ, LG. All authors participate in drafting the article.

Conflicts of interest

The authors declare no conflicts of interest.

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