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# Study of Anti-nociceptive Role of the *Manna of Hedysarum* and the Neurotransmitter Systems Involved in Mice

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## Abstract

**BACKGROUND:** Pain is an unpleasant experience that serves as a survival mechanism and is mediated via the central and peripheral nervous systems. *Manna of hedysarum*, also called *Persian Manna* or *Taranjebin*, is known to have medical properties in Persian traditional medicine.

**OBJECTIVES:** The main purpose of the current paper is to determine the possible antinociceptive effect of *Manna of hedysarum* as well as the neurotransmitter systems involved, in mice.

**METHODS:** The first experiment was designed to reveal the effective dose of *Manna of hedysarum*. Adult male albino mice were injected with *Manna of Hedysarum* (100, 200, and 400 mg/kg) Ethanolic Extract (MHEE) or morphine (5 mg/kg). In experiment 2, MHEE (400 mg/kg), naloxone (2 mg/kg), and MHEE (400 mg/kg) plus naloxone (2 mg/kg) were injected. Experiments 3-5 were similar to experiment 2, except that naloxone was replaced with L-NG-Nitro Arginine Methyl Ester (10 mg/kg), cimetidine (12.5 mg/kg), and cyproheptadine (4 mg/kg). Then the formalin test was performed, and the paw licking time was measured.

**RESULTS:** Based on the findings, MHEE reduced the pain response in a dose-dependent manner ($P<0.05$). The co-injections of MHEE with mentioned antagonists significantly decreased the antinociceptive effect of MHEE on the licking and biting time of the injected paw ($P<0.05$).

**CONCLUSIONS:** These findings suggest that MHEE has an antinociceptive effect in mice and possibly acts on opioidergic, nitrergic, histaminergic and serotonergic systems.

**KEYWORDS:** Anti-nociceptive, Histaminergic, *Manna of hedysarum*, Mice, Nitrergic, Opioidergic, Serotonergic system

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## Introduction

Pain sensation is a defense mechanism that has evolved to protect tissues against actual or potential damage; obviously, it has played an important role in the survival of animals. Pain is also a symptom in many diseases, which is an important alert to notify that something is going or has already gone wrong in the organism. However, persisting pain may lead to chronic diseases and cause some changes to the central nervous system or the peripheral tissues. Nociceptive signaling dysfunction at different levels of the nervous system can be the major cause of pathological pain (Yam *et al*., 2018). Pathological pain has a devastating effect on the personal, social, and interpersonal aspects of a human's life. Dealing with pathological pain imposes a huge economic burden on the healthcare system each year worldwide. Globally, it has been estimated that 1 in 5 adults suffers from pain and that another 1 in 10 adults is diagnosed with chronic pain each year (Goldberg and McGee, 2011).

Analgesic agents such as opioid analgesics and nonsteroidal anti-inflammatory drugs have known side effects. This has persuaded researchers to become interested in examining new natural analgesic agents that lack such side effects. Among these novel natural analgesics, herbal medicine has received increasing attention. It is one of the most commonly sought forms of Complementary and alternative medicine, which has attracted growing interest from researchers and has largely been accepted (Jahromi *et al*., 2021). The herbal market in Persia has a long historical background. Manna is a byproduct of insect activity on host plants. Different types of Manna are available in the Persian herbal market. One of the best-known products in this market with high economic value is the *Manna of hedysarum*, which is secreted on camel's thorn (*Alhagi Maurorum*) bushes. *Manna of hedysarum* has various names such as Taranjebin, Persian Manna, Tar-angabin, Al hagi manna, or camel's thorn manna, to name a few. In English, this Manna is known as *Alhagi manna*, *Caspian manna*, *Merniabin manna*, and *Manna of Hedysarum*. (Hamedi *et al*., 2015).

In Persian traditional medicine, various pharmacological properties have been linked with *Manna of hedysarum,* including antioxidant, anti-inflammatory, and antipyretic ones. It has also been used to treat liver diseases, hyperbilirubinemia states, as a laxative for children, gastrointestinal diseases, joint pains, and blood purifiers in various viral diseases such as chicken-pox measles, and mumps (Ansari, 2019). It has also been used to treat stomach aches, neurological disease, kidney stones (Mardaninejad *et al*., 2013), rubella, cough, pectoral aches, and vomiting. It has also been used as a thirst quencher (Yazdanparats *et al*., 2014). Many pharmacological properties of Manna have been attributed to its saccharriferous compound. A 5% humid *Manna of hedysarum* contains 47.7% melzitoze sugar, 26.44% sucrose, and 11.5% fructose (sharif, 2013). Recently, high selenium accumulating quality of *Manna of hedysarum* has also been discovered (Ziarati and Hochwimmer, 2018). Despite wide administration of this type of Manna by traditional Persian practitioners or by Iranian folk medicine, little has been done to evaluate its safety or provide evidence for its widely-claimed therapeutic properties. This study aims to evaluate the analgesic effect of *Manna of hedysarum*. According to the current literature, this will be the first study conducted on this concept.

## Materials and Methods

### Experimental Animals and Ethical Aspects

Animal care and the experimental steps were performed according to the criteria of care and use of institutional Animals Medical Sciences Ethics Committee of Science and Research University, Tehran, Iran (Ethical code: IR.IAU.SRB.REC.1400.029). The protocol and the experiments followed the guidelines on Ethical Standards for investigating experimental pain in animals (Zimmermann, 1983; Kim *et al*., 2014). In this research, 105 adult male NMRI mice within a weight range of 25−30 grams were used. The animals were housed in a room with a constant temperature (23°C±1) and a 12-hour light/dark cycle in standard cages (8-10 in each cage). Fresh water and chow pellets were allowed with no limitations. The animals were acclimatized to the laboratory environment for one week before performing the experiments, and then the formalin test was performed to determine the antinociceptive effect of *Manna of hedysarum*. To achieve this goal, five experiments were designed with 4-5 groups in

each (n = 6 in each group). The researchers were blinded by the experimental conditions as the requirement of a blind experiment. The experiments were carried out during the light cycle between 8 AM to 2 PM. Thirty minutes before testing, the animals were placed individually in a transparent Plexiglas box (30 × 30 × 25 $cm^3$) equipped with a mirror at a 45° angle below the chamber, which served as an observation chamber.

### Plant Extraction

Manna of hedysarum was obtained from a herbal market in Tehran, Iran. The blended Manna was immediately resolved in 80% ethanol (in a ratio of 1:12) and then mixed for 72 hours on a basic shaker (IKA KS 260, Germany). Then, it was filtered and concentrated with a rotary evaporator at a temperature below 50°C (IKA-WERKE, Germany) for 1.5 hours. Finally, the liquid was dried for 24 hours at 50°C, and the resulting powder was mixed with distilled water as a solvent. The mice were injected intraperitoneally with MHEE.

### Drugs

Morphine sulfate, Naloxone, L-NG-Nitro Arginine Methyl Ester (L-NAME), Cimetidine, and Cyproheptadine were purchased from Sigma Chemical Co. (St. Louis, USA), and formalin was purchased from Merck (Darmstadt, Germany). The MHEE and all other drugs were dissolved in distilled water. All drugs were injected intraperitoneally (IP).

### Formalin Test

In the first experiment, to determine the effective dose of the extract, animals in the control group were treated with normal saline solution (IP); in groups 2-4, animals were injected with MHEE (100 mg/kg, 200 mg/kg, 400 mg/kg), and in group 5 morphine was injected (5 mg/kg); after 30 minutes, in each group, the mice were injected with formalin solution (10 µL, 1%) into the right hind paw. The test was conducted following the guideline delineated by Hunskaar and Hole (Hunskaar and Hole, 1987). The animals were then placed back in the observation chamber (described above), and the nociceptive response was evaluated by measuring the time spent licking the injected paw and expressed as the total licking time in the first phase (phase I; 0–5 min) and the 2nd phase (phase II; 15–30 min) after formalin injection (Azhdari-Zarmehri *et al*., 2014).

In experiments 2-5, the combination of MHEE and antagonists was injected to assess the neurotransmitter systems. Therefore, the antagonists and MHEE were given 30 minutes and 15 minutes before the formalin challenge, respectively.

In experiment two, animals in the control group were injected (IP) with normal saline, and groups 2-4 were injected with MHEE (400 mg/kg), naloxone (2 mg/kg), and MHEE (400 mg/kg) plus naloxone (2 mg/kg). Then, the nociceptive response was recorded after conducting the formalin test.

In the third experiment, normal saline, MHEE (400 mg/kg), L-NAME (10 mg/kg), and MHEE (400 mg/kg) together with L-NAME (10 mg/kg) were injected. Then, the nociceptive response was evaluated.

The injections of experiment four were as follows: normal saline, MHEE (400 mg/kg), cimetidine (12.5 mg/kg), and MHEE (400 mg/kg) plus cimetidine (12.5 mg/kg). Then, the nociceptive response was recorded.

In experiment five, the mice received IP injections of normal saline, MHEE (400 mg/kg), cyproheptadine (4 mg/kg), and MHEE (400 mg/kg) plus cyproheptadine (4 mg/kg). Then, the nociceptive response was recorded. In this study, the sub-effective doses of antagonist drugs were used, and the applied dose for each antagonist was chosen based on previous studies (Zendehdel *et al*., 2015; Lin *et al*., 2016).

### Statistical Analysis

The data were analyzed by one-way analysis of variance (ANOVA) using SPSS 16.0 and expressed as mean ± standard error (SE). Data from the first and the 2nd phases were analyzed separately because the formalin test caused a distinct biphasic nociceptive response. For treatments showing the main effect by ANOVA, the analysis was followed by a Tukey post-hoc test. The P-value< 0.05 was considered to be statistically significant.

## Results

Figure 1 demonstrates the antinociceptive effect of MHEE. As illustrated, MHEE significantly decreased the time spent licking and biting in injected paw compared to the control group ($P< 0.05$) in a dose-dependent manner. The maximum analgesia was observed at a dose of 400 mg/kg of MHEE in

the first and the 2nd phases ($P$<0.05). Pretreatment with naloxone caused a reversal of MHEE-induced analgesic activity, as demonstrated by an increase in the paw licking response compared with the MHEE-treated group ($P$<0.05), as shown in Figure 2.

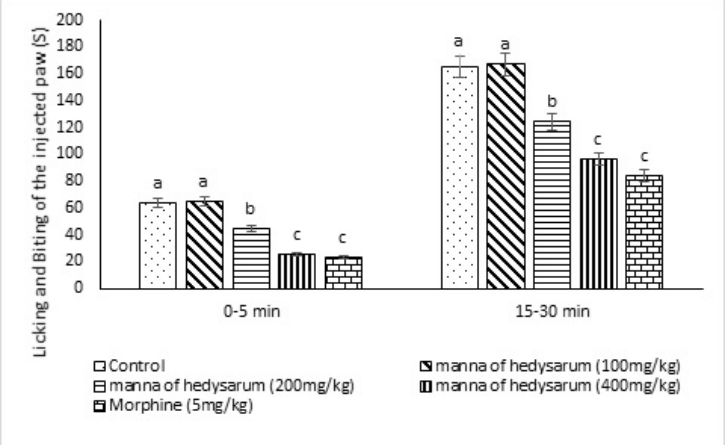


**Figure 1.** Effect of the *Manna of hedysarum* ethanolic extract on licking and biting the injected paw in male mice (n = 30). Data are expressed as mean ± SE. Different superscripts (a-c) indicate significant differences between groups ($P$<0.05).

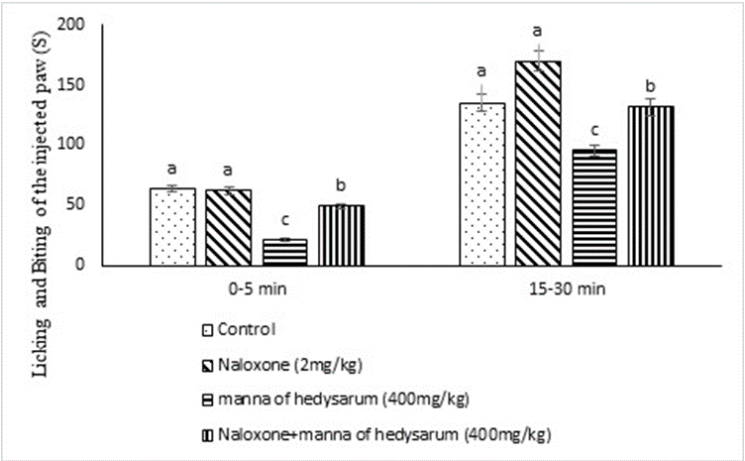


**Figure 2.** Evaluation of the participation of the opioidergic system on the antinociceptive effect of MHEE in the formalin-induced licking model. The animals were pretreated with naloxone (opioid receptor antagonist) 15 minutes before IP administration of MHEE (400 mg/kg). The results are expressed as mean ± SE of the time the animals spent licking the formalin-injected paw (n=30). Different superscripts (a-c) indicate significant differences between groups ($P$<0.05).

Figure 3 shows that L-NAME did not demonstrate any analgesic activity ($P$>0.05). A combination of L-NAME plus MHEE reduced the analgesic activity of MHEE ($P$<0.05; Figure 3).

Cimetidine did not affect the nociceptive behavior ($P$>0.05). Please see Figure 4. Pretreatment with Cimetidine diminished the analgesic activity of MHEE in both phases ($P$<0.05), as is shown in Figure 4.

Based on Figure 5, Cyproheptadine did not affect the nociceptive behavior ($P$>0.05). Pretreatment with Cyproheptadine significantly decreased the analgesic activity of MHEE ($P$<0.05; Figure 5).

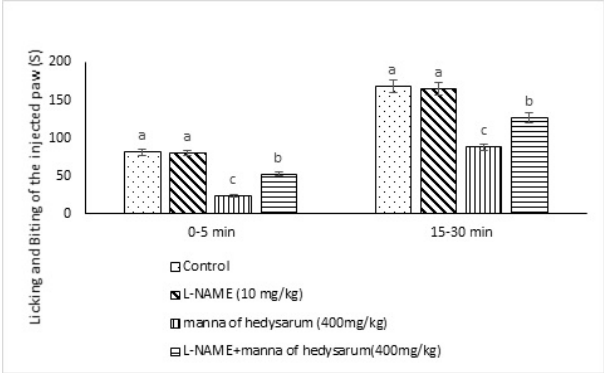


**Figure 3.** Evaluation of the participation of the nitrergic system on the antinociceptive effect of MHEE in the formalin-induced licking model. The animals were pretreated with L-NAME (antagonist of nitric oxide synthase) 15 minutes before IP administration of MHEE (400 mg/kg). The results are expressed as mean ± SE of the time the animals spent licking the formalin-injected paw (n=30). Different superscripts (a-c) indicate significant differences between the groups ($P$<0.05).

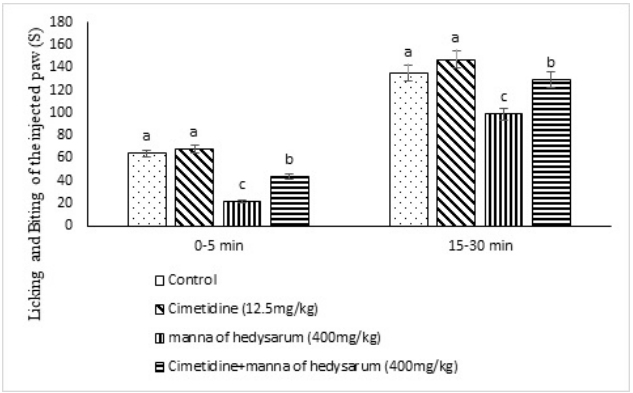


**Figure 4.** Evaluation of the participation of the histaminergic system on the antinociceptive effect of MHEE in the formalin-induced licking model. The animals were pretreated with Cimetidine (histamine H2-receptor antagonist) 15 minutes before IP administration of MHEE (400 mg/kg). The results are expressed as mean ± SE of the time the animals spent licking the formalin-injected paw (n=30). Different superscripts (a-c) indicate significant differences between groups ($P$< 0.05).

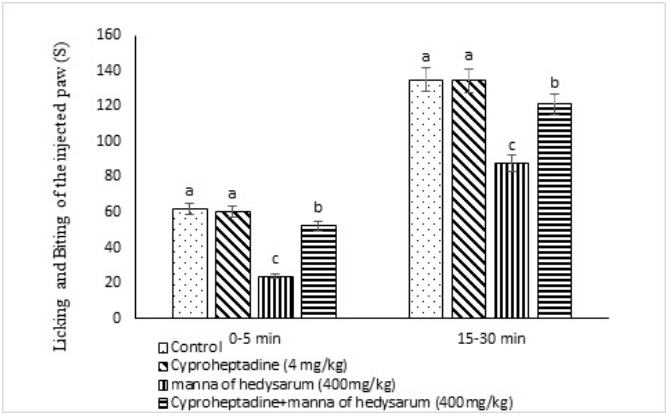


**Figure 5.** Evaluation of the participation of the serotonergic system on the antinociceptive effect of MHEE in the formalin-induced licking model. The animals were pretreated with Cyproheptadine (serotonergic receptor antagonist) 15 minutes before IP administration of MHEE (400 mg/kg). The results are expressed as mean ± SE of the time the animals spent licking the formalin-injected paw (n=30). Different superscripts (a-c) indicate significant differences between groups ($P$<0.05).

## Discussion

The present study aimed to determine the possible antinociceptive effect of MHEE in vivo since one of the medical properties of *Manna of hedysarum*, as mentioned in the literature, is its analgesic effect (Mardaninejad *et al*., 2013; Tavassoli *et al*., 2020). Based on our knowledge up to the time of preparing this manuscript, no clinical and in vivo studies have investigated this effect. The formalin test was conducted to induce the pain response in this study. In this test, formalin acts as an irritant compound that results in inflammatory pain (Kaliyaperumal *et al*., 2020). Formalin injection produces a biphasic response. The first phase (0–5 min), which is also known as the neurogenic phase, is due to the activation of C-fibers, and the 2nd phase (inflammatory phase), occurs between 15 and 30 minutes after formalin injection and is mediated by the release of a combination of inflammatory mediators. Attenuation of the nociceptive response is observed during the interphase (5-15 minutes) (Muley *et al*., 2016). Based on the experiments in our study, MHEE suppressed the nociceptive response, in a dose-dependent manner, in both phases. In this study, morphine (5 mg/kg) was used as a reference drug, and the selected dose was based on previous reports (Mohammadifard and Alimohammadi, 2018).

*Manna of hedysarum* contains high levels of selenium compounds (Ziarati and Hochwimmer, 2018). Selenium (Se) is an essential trace element that plays a pivotal role in the cell's antioxidant defense system. Antioxidants reduce inflammation by neutralizing excessive free radicals (Arulselvan *et al*., 2016). The analgesic effect of MHEE seen in the second phase of the formalin test may be due to the amount of Se content. However, antinociceptive activity was seen in both phases. Therefore, regarding the present study results, it might be suggested that besides Se, there are also other mechanisms involved in MHEE-induced antinociception activity.

To investigate the neurotransmitter systems involved in *Manna of hedysarum* antinociceptive activity, the MHEE reaction was examined in the formalin test with opioidergic, nitrergic, histaminergic, and serotonergic receptors.

As observed, injection of naloxone did not demonstrate any analgesic activity in the first and the 2nd phases (Figure 2); this is consistent with previous studies (Azhdari-Zarmehri *et al*., 2014). Naloxone is a competitive antagonist at mu, kappa, and delta receptors (Whalen *et al*., 2019). Opioid receptors are contributed to antinociception. Pretreatment with naloxone decreased the analgesic effect of MHEE (Figure 2). Therefore, we hypothesized that the analgesic activity of MHEE is related to the opioid system.

The other drug used in this research, L-NG-Nitro Arginine Methyl Ester (L-NAME), is a non-specific nitric oxide synthase (NOS) inhibitor (Liu *et al*., 2019). Nitric oxide (NO) is an important neurotransmitter with an essential role in acute and chronic pain states at central and peripheral levels. NO plays a complex and diverse role in modulating the nociceptive process. In the dorsal horn of the spinal cord, NO contributes to the development of central sensitization. Moreover, the Subplantar injection of irritant compounds increases the NO level in the injected site, and pretreatment with L-NAME prevented the increase in the pro-inflammatory cytokines.

Additionally, evidence demonstrates that NO induces analgesia and is involved in the peripheral antinociceptive effect of analgesic drugs (Cury *et al*., 2011). As can be seen, co-administration of L-NAME and MHEE decreased the antinociceptive effect of MHEE (Figure 3). This information may suggest that the antinociceptive activity of the *Manna of hedysarum* is mediated through the nitrergic system.

Cimetidine, a specific competitive histamine $H_2$-receptor antagonist, was injected to observe the histaminergic system's role in the antinociceptive activity of *Manna of hedysarum*. Histamine plays a dual role in the processing of nociceptive information, that is, antinociceptive activity in the CNS versus nociceptive activity in the PNS. In the PNS, tissue injuries lead to histamine release and result in pain hypersensitivity through the sensitization of polymodal nociceptors (Obara *et al*., 2020). Co-administration of Cimetidine and MHEE also decreased the antinociceptive effect of MHEE. Accordingly, the *Manna of hedysarum* antinociceptive activity might be associated with the histaminergic system (Hasanein 2011).

Cyproheptadine is a potent competitive antagonist of serotonin and histamine $H_1$ receptors (Maddison *et al*., 2008). Serotonin plays a complex role in the perception of pain. It is assumed that serotonin can both inhibit and promote pain perception by different physiological mechanisms (Marks *et al*., 2009). Co-administration of Cyproheptadine and MHEE also decreased the antinociceptive effect of MHEE. Therefore, the analgesic activity of MHEE can be attributed to the serotonergic system.

In the current study, no procedure was applied to identify the ingredients of MHEE and the results of the previous analysis of *Manna of hedysarum* were used (Sharif, 2013; Ziarati and Hochwimmer, 2018). This can be considered a limitation in this study.

In summary, MHEE has antinociceptive activity in mice, mediated via opioidergic, nitrergic, histaminergic, and serotonergic systems; however, the precise mechanism of the activities mentioned above has to be clarified in the future studies. In future studies, these results can be used as a guideline to determine the antinociceptive mechanism of action of Manna of hedysarum.

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## Conflict of Interest

The authors declared that there is no conflict of interest.

## References

Ansari, S. (2020). Medicinal characteristics and therapeutic application of Manna/Taranjabeen (Alhagi pseudalhagi) in Unani medicine. *Annals of Ayurvedic Medicine*, *8*(3), 126-126.

Arulselvan, P., Fard, M. T., Tan, W. S., Gothai, S., Fakurazi, S., Norhaizan, M. E., & Kumar, S. S. (2016). Role of antioxidants and natural products in inflammation. Oxidative Med Cell Longev 2016: 5276130. [DOI:10.1155/2016/5276130] [PMID] [PMCID]

Azhdari-Zarmehri, H., Mohammad-Zadeh, M., Feridoni, M., & Nazeri, M. (2014). Termination of nociceptive bahaviour at the end of phase 2 of formalin test is attributable to endogenous inhibitory mechanisms, but not by opioid receptors activation. *Basic and Clinical Neuroscience*, *5*(1), 48.

Khan, M., Jatana, M., Elango, C., Paintlia, A. S., Singh, A. K., & Singh, I. (2006). Cerebrovascular protection by various nitric oxide donors in rats after experimental stroke. *Nitric Oxide*, *15*(2), 114-124. [DOI:10.1016/j.niox.2011.06.004] [PMID]

Goldberg, D. S., & McGee, S. J. (2011). Pain as a global public health priority. *BMC Public Health*, *11*(1), 1-5. [DOI:10.1186/1471-2458-11-770] [PMID] [PMCID]

Hamedi, A., Farjadian, S., & Karami, M. R. (2015). Immunomodulatory properties of Taranjebin (Camel's Thorn) manna and its isolated carbohydrate macromolecules. *Journal of Evidence-based Complementary & Alternative Medicine*, *20*(4), 269-274. [DOI:10.1177/2156587215580490] [PMID]

Hasanein, P. (2011). Two histamine H2 receptor antagonists, zolantidine and cimetidine, modulate nociception in cholestatic rats. *Journal of Psychopharmacology*, *25*(2), 281-288. [DOI:10.1177/0269881109106912] [PMID]

Hunskaar, S., & Hole, K. (1987). The formalin test in mice: dissociation between inflammatory and non-inflammatory pain. *Pain*, *30*(1), 103-114. [DOI:10.1016/0304-3959(87)90088-1]

Jahromi, B., Pirvulescu, I., Candido, K. D., & Knezevic, N. N. (2021). Herbal medicine for pain management: efficacy and drug interactions. *Pharmaceutics*, *13*(2), 251. [DOI:10.3390/pharmaceutics13020251] [PMID] [PMCID]

Johnson, A. C., & Greenwood-Van Meerveld, B. (2014). Stress-induced pain: a target for the development of novel therapeutics. *Journal of Pharmacology and Experimental Therapeutics*, *351*(2), 327-335. [DOI:10.1124/jpet.114.218065] [PMID] [PMCID]

Kaliyaperumal, S., Wilson, K., Aeffner, F., & Dean Jr, C. (2020). Animal models of peripheral pain: Biology review and application for drug discovery. *Toxicologic Pathology*, *48*(1), 202-219. [DOI:10.1177/0192623319857051] [PMID]

Kim, D. H., Sung, B., Kang, Y. J., Jang, J. Y., Hwang, S. Y., Lee, Y., ... & Kim, N. D. (2014). Anti-inflammatory effects of betaine on AOM/DSS-induced colon tumorigenesis in ICR male mice. *International Journal of Oncology*, *45*(3), 1250-1256. [DOI:10.3892/ijo.2014.2515] [PMID]

Lin, J. C., Lee, M. Y., Chan, M. H., Chen, Y. C., & Chen, H. H. (2016). Betaine enhances antidepressant-like, but blocks psychotomimetic effects of ketamine in mice. *Psychopharmacology*, *233*(17), 3223-3235. [DOI:10.1007/s00213-016-4359-x] [PMID]

Liu, T., Zhang, M., Mukosera, G. T., Borchardt, D., Li, Q., Tipple, T. E., ... & Blood, A. B. (2019). L-NAME releases nitric oxide and potentiates subsequent nitroglycerin-mediated vasodilation. *Redox biology*, *26*, 101238. [DOI:10.1016/j.redox.2019.101238] [PMID] [PMCID]

Maddison, J. E., Page, S. W., & Church, D. B. (Eds.). (2008). *Small animal clinical pharmacology* (Vol. 5). Elsevier Health Sciences.

Mardaninejad, S., Janghorban, M., & Vazirpour, M. (2013). Collection and identification of medicinal plants used by the indigenous people of Mobarakeh (Isfahan), southwestern Iran. *Journal of Medicinal Herbs,*, *4*(1), 23-32.

Marks, D. M., Shah, M. J., Patkar, A. A., Masand, P. S., Park, G. Y., & Pae, C. U. (2009). Serotonin-norepinephrine reuptake inhibitors for pain control: premise and promise. *Current Neuropharmacology*, *7*(4), 331-336. [DOI:10.2174/157015909790031201] [PMID] [PMCID]

Mohammadifard, F., & Alimohammadi, S. (2018). Chemical composition and role of opioidergic system in antinociceptive effect of Ziziphora clinopodioides essential oil. *Basic and Clinical Neuroscience*, *9*(5), 357. [DOI:10.32598/bcn.9.5.357] [PMID] [PMCID]

Muley, M. M., Krustev, E., & McDougall, J. J. (2016). Preclinical assessment of inflammatory pain. *CNS Neuroscience & Therapeutics*, *22*(2), 88-101.. [DOI:10.1111/cns.12486] [PMID] [PMCID]

Obara, I., Telezhkin, V., Alrashdi, I., & Chazot, P. L. (2020). Histamine, histamine receptors, and neuropathic pain relief. *British Journal of Pharmacology*, *177*(3), 580-599. [DOI:10.1111/bph.14696] [PMID] [PMCID]

Sharif, M. R. (2015). The effect of Manna of hedysarum prescription on the decrease of bilirubin level in lcteric neonates. *Biomedical and Pharmacology Journal*, *6*(2), 363-367. [DOI:10.13005/bpj/426]

Tavassoli, A. P., Anushiravani, M., Hoseini, S. M., Nikakhtar, Z., Baghdar, H. N., Ramezani, M., ... & Emami, S. A. (2020). Phytochemistry and therapeutic effects of Alhagi spp. and tarangabin in the Traditional and modern medicine: a review. *Journal of Herbmed Pharmacology*, 86-104. [DOI:10.34172/jhp.2020.13]

Trescot, A. M., Datta, S., Lee, M., & Hansen, H. (2008). Opioid pharmacology. *Pain Physician*, *11*(2 Suppl), S133-53. [DOI:10.36076/ppj.2008/11/S133]

Whalen, K., Feild, C., Radhakrishnan, R. (2019). *Lippincot Illustrated Reviews: Pharmacology*, 7th ed. Wolters Kluwer Pub. Philadelphia, Baltimore, New York... ISBN(10): 149638413X

Yam, M. F., Loh, Y. C., Tan, C. S., Khadijah Adam, S., Abdul Manan, N., & Basir, R. (2018). General pathways of pain sensation and the major neurotransmitters involved in pain regulation. *International Journal of Molecular Sciences*, *19*(8), 2164. [DOI:10.3390/ijms19082164] [PMID] [PMCID]

Yazdanparats, S., Ziarati, P., & Asgarpanah, J. (2014). Nutritive values of some Iranian Manna. *Biosciences Biotechnology Research Asia*, *11*(2), 1025-1029. [DOI:10.13005/bbra/1378]

Zendehdel, M., Taati, M., Amoozad, M., & Hamidi, F. (2012). Antinociceptive effect of the aqueous extract obtained from Foeniculum vulgare in mice: the role of histamine H1 and H2 receptors.

Zendehdel, M., Torabi, Z., & Hassanpour, S. (2015). Antinociceptive mechanisms of Bunium persicum essential oil in the mouse writhing test: role of opioidergic and histaminergic systems. *Veterinarni Medicina*, *60*(2), 63. [DOI:10.17221/7988-VETMED]

Ziarati, P., & Hochwimmer, B. (2018). The Medical Geology and Discovery of Taranjebin Manna as a Hyper Selenium Accumulator; Biomedical and Ethno-Medical Efficacy Links to Calc-alkaline and Alkalic Tethyan Magmatic Arcs. *Journal of Agricultural Science and Food Research*, *9*, 234.

Zimmermann, M. (1983). Ethical guidelines for investigations of experimental pain in conscious animals. *Pain*, *16*(2), 109-110. [DOI:10.1016/0304-3959(83)90201-4

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# مطالعه اثرات ضد دردی عصاره ترنجبین و شناسایی سیستم‌های نوروترانسمیتری دخیل در موش سوری

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**زمینه مطالعه:** درد یک تجربه ناخوشایند است که به‌عنوان مکانیسم برای بقا مطرح هست و توسط سیستم عصبی مرکزی و سیستم عصبی محیطی میانجی‌گری می‌شود. ترنجبین که به اسامی دیگری از جمله مان ایرانی و مان گیاه خارشتر نیز شناخته می‌شود، خواص دارویی متفاوتی در طب سنتی ایران دارد.

**هدف:** در مطالعه حاضر اثرات ضد دردی عصاره ترنجبین و سیستم‌های نوروترانسمیتری دخیل، در موش سوری بررسی شد.

**روش کار:** آزمایش اول به منظور تعیین دوز موثر عصاره اتانولی ترنجبین صورت گرفت. در این آزمایش دوز۱۰۰ mg/kg، ۲۰۰ mg/kg و ۴۰۰mg/kg و مورفین (۵mg/kg) به صورت داخل صفاقی به موش‌ها تزریق شد. در آزمایش‌های ۲-۵ برای شناسایی سیستم‌های نوروترانسمیتری از تزریق دوز موثر عصاره ترنجبین همراه آنتاگونیست‌های مختلف استفاده شد و در هر آزمایش از تزریق زیرپوستی فرمالین در کف پای راست به منظور تست درد استفاده شد و مدت زمان لیسیدن و جویدن پا ثبت شد. به‌منظور تجزیه و تحلیل داده‌ها، نتایج حاصل توسط آنالیز واریانس یک طرفه مورد تجزیه و تحلیل قرار گرفته و برای بررسی مقایسات میانگین بین گروه‌ها در سطح معنی‌داری ($P\leq$۰/۰۵) از تست چند دامنه‌ای توکی استفاده گردید.

**نتایج:** براساس نتایج به‌دست‌آمده ترنجبین باعث کاهش پاسخ درد به‌صورت وابسته به دوز می‌شود. تزریقات ترنجبین همراه آنتاگونیست‌های ذکرشده به‌طور معنی‌داری موجب کاهش اثر ضد دردی ترنجبین و افزایش مدت زمان جویدن و لیسیدن کف پا در موش‌ها شدند.

**نتیجه‌گیری نهایی:** با توجه به نتایج به‌دست‌آمده، عصاره اتانولی ترنجبین اثر ضد دردی وابسته به دوز دارد و باعث کاهش هر دو فاز اول و دوم درد می‌شود و اثر ضد دردی خود را از مسیرهای اپیوئیدرژیک، هیستامینرژیک، نیترارژیک و سروتونرژیک میانجی‌گری می‌کند.

**واژه‌های کلیدی:** اثر ضد دردی، ترنجبین، سروتونرژیک، هیستامینرژیک، نیترارژیک، اپیوئیدرژیک، موش

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