Original Article

Anti-nociceptive Activity of the Safflower (*Carthamus tinctorius* L.) in Mice

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ABSTRACT

Background: Pain is a traditional indication of an inflammatory reaction, manifesting allodynia and hyperalgesia. *Carthamus tinctorius* L. has demonstrated various biological activities.

Objectives: This study aimed to determine the anti-nociceptive activity of the *C. tinctorius* L. in mice.

Methods: A total of 105 adult male NMRI mice were randomly assigned to participate in five separate experiments, each consisting of four groups. In the initial trial, the mice were administered saline, an extract derived from *C. tinctorius* L. (100, 200 and 400 mg/kg) and morphine (5 mg/kg). In the second trial, the subjects were treated with saline, naloxone (2 mg/kg), extract of *C. tinctorius* L. (400 mg/kg), and a combination of extracts of *C. tinctorius* L. and naloxone. In trials 3-5, L-Name (10 mg/kg), cyproheptadine (4 mg/kg) and flumazenil (5 mg/kg) were administered instead of naloxone. Formalin was then injected, and paw-licking time (pain sense) was recorded.

Results: According to the results, *C. tinctorius* L. exhibited a decrease in pain response compared to the control animals ($P<0.05$). Injection of naloxone in combination with *C. tinctorius* L. reduced the pain response during the formalin test ($P<0.05$). Injection of L-NAME combined with *C. tinctorius* L. led to increased pain response during the formalin test ($P<0.05$). Cyproheptadine was administered combined with *C. tinctorius* L. and pain response was reduced during the formalin test ($P<0.05$). Injection of flumazenil combined with *C. tinctorius* L. reduced pain response during the formalin test ($P<0.05$).

Conclusion: These results suggested that the antinociceptive activity of *C. tinctorius* L. is mediated via the opioidergic, nitrergic, serotonergic and GABAergic systems in mice.

Keywords: Antinociceptive, Safflower, Nitrergic, Serotonergic, GABAergic

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Introduction

Pain is a traditional indication of an inflammatory reaction resulting in the manifestation of allodynia or hyperalgesia, which is referred to as nociception. Consequently, a range of ailments, such as back pain, rheumatoid arthritis, and recurrent migraines, can arise due to insufficient management of the inflammatory process (Chy et al., 2021). Inflammation triggers the activation of peripheral nerve fibers and causes alterations in local blood circulation and permeability of blood vessels (Farahani et al., 2021). Moreover, immune cells that are activated during inflammation release proalgesic agents, such as tumor necrosis factor-α, interleukins (IL-6, IL-8, IL-1β), protons, nerve growth factor and prostaglandins, which contribute to the occurrence of both inflammatory and neuropathic pain (Meymandi et al., 2019).

Effective management of pain, particularly in cases of prolonged duration, has remained an unfulfilled medical necessity in recent years. While pharmacotherapy centered on the usage of opioids remains the most potent approach for addressing moderate to severe pain, the ratio between the benefits and risks associated with this treatment is not optimal due to the occurrence of frequent and severe adverse effects (Dumitrascuta et al., 2021; Jadgalradeh et al., 2023). The exponential surge in medical utilization and misapplication of opioids, coupled with the escalating number of fatalities resulting from overdose and the prevalence of opioid-use disorders, has contributed to the present-day opioid crisis (Pasternak et al., 2020). Consequently, diligent research endeavors are imperative to surmount the limitations of current therapeutic interventions, with the ultimate goal of enhancing treatment effectiveness and curtailing complications (Günther et al., 2018). Due to the adverse effects of the prolonged use of synthetic medications to treat painful conditions and inflammation, numerous studies have explored various plant extracts and their active compounds to evaluate their potential to exert antinociceptive and anti-inflammatory effects.

Safflower, a plant known scientifically as *Carthamus tinctorius* L. and belonging to the Asteraceae family, has a long history of traditional medicinal and edible use. Safflower thrives primarily in arid climates, particularly in Southern Asia, China, India, Iran and Egypt. It was introduced to Western countries, such as Italy, France, Spain, and the United States, between the 5th and 14th centuries (Miakhil et al., 2024). In Iran, it is known as "Golrang" and has been extensively cultivated for its flower petals, which contain red and orange pigments (Wang et al., 2014). Safflower oil, derived from *C. tinctorius* L., is highly valued for its nutritional composition. It comprises approximately 70% polyunsaturated fatty acid, specifically linoleic acids, 10% monounsaturated oleic acid, and minimal amounts of stearic acid. *C. tinctorius* L. has demonstrated various biological activities, including antimicrobial, antithrombotic, anticoagulant, antinociceptive, antitumor, and anti-inflammatory properties. Previous studies have extensively examined the phytochemical composition and biological characteristics of florets of *C. tinctorius* L. (Kim et al. 2023). In Iranian folk medicine, safflower has been employed to treat cerebrovascular disease and heart disease. Moreover, Safflower exhibits notable purgative, analgesic and antipyretic properties, making it beneficial for patients with poisoning (Gautam et al., 2014).

Several studies have illustrated that *C. tinctorius* L. exhibits an anti-inflammatory influence. Among the multitude of pain models, formalin-induced pain is considered to be caused by inflammation (Hong et al., 2020). Based on the literature, no report exists on the antinociceptive activity of *C. tinctorius* L. in mice. Thus, this study aimed to determine the antinociceptive activity of *C. tinctorius* L. using the formalin test in mice.

Materials and Methods

Animals

In this study, 105 adult male NMRI mice weighing 25±3 g were maintained in a controlled laboratory environment that provided unrestricted access to pellets and water. The animals were randomly assigned to participate in five experiments, each consisting of four groups (n=5).

Extraction and chemicals

C. tinctorius L. flowers were fully dried at room temperature and powdered using a mechanical mill away from sunlight. Subsequently, the extraction process was carried out using a maceration method with a 70% methanolic solvent. This extraction procedure was replicated thrice, with each iteration lasting 24 hours. The obtained extracts were thoroughly desiccated using a vacuum-assisted rotary evaporator, ensuring that the temperature did not exceed 45 ˚C. The resultant extracts were preserved in a refrigerated environment until they were ready for use (Hosseinzadeh et al. 2009). Morphine, naloxone, L-NAME (NO inhibitor), cyproheptadine (serotonergic receptor antagonist) and flumazenil (GABAergic receptor antagonist) purchased from Sigma (St.

Louis, MO, USA). Ethanol and formalin were purchased from Merck (Darmstadt, Germany). The drugs were first dissolved in saline and then intraperitoneally injected (0.5 mL). The dosages of the drugs were obtained from previous reports (Wang et al., 2014; Hassanpour et al., 2020; Kim et al., 2023).

Formalin test

In the initial trial, mice were subjected to the administration of saline, an extract derived from *C. tinctorius* L. (100 mg/kg), an extract derived from *C. tinctorius* L. (200 mg/kg), an extract of *C. tinctorius* L. (400 mg/kg), and morphine (5 mg/kg). After thirty minutes, 50 µL of 1% formalin solution was injected into the plantar surface of the right paw (Figure 1). In the second trial, the subjects were treated with saline, naloxone (2 mg/kg), an extract derived from the plant *C. tinctorius* L. (400 mg/kg), or a combination of an extract of *C. tinctorius* L. and naloxone (Figure 2). In cases where two injections were administered, the subjects primarily received the antagonist, followed by *C. tinctorius* L. after 15 minutes. Additionally, 15 minutes later, formalin was injected, and the subsequent pain response was determined by assessing the time spent licking and biting the injected paw. In the third trial, the mice were intraperitoneally injected with saline, L-NAME (10 mg/kg), an extract of *C. tinctorius* L. (400 mg/kg) and a combination of an extract of *C. tinctorius* L. and L-NAME (Figure 3). In the fourth trial, the mice were intraperitoneally injected with saline, cyproheptadine (4 mg/kg), an extract of *C. tinctorius* L. (400 mg/kg), and a combination of an extract of *C. tinctorius* L. and cyproheptadine (Figure 4). In the fifth trial, the mice were intraperitoneally injected with saline, flumazenil (5 mg/kg), an extract of *C. tinctorius* L. (400 mg/kg) and a combination of an extract of *C. tinctorius* L. and flumazenil (Figure 5). The analgesic effect of *C. tinctorius* L. was assessed utilizing the formalin test, as described by Dubuisson and Dennis (1977), with certain modifications. The procedure involved injecting 20 µL formalin (0.5% formaldehyde in saline) into the plantar region of the right hind paw. Each animal was subsequently placed within a transparent plastic enclosure, and the time spent licking and/or biting the injected hind paw was recorded at 5-minute intervals over a 30-minute observation period. The formalin test comprises two distinct phases: an initial phase resulting from a direct impact on nociceptors, lasting for the first 5 minutes (neurogenic pain) and a later phase resulting from a direct impact of inflammatory mediators, lasting from 15 to 30 minutes (inflammatory pain) after formalin injection (Mota et al., 2011).

Statistical analysis

Data were analyzed using the SPSS software, version 22. The analysis employed a one-way analysis of variance followed by Tukey's post-hoc test. All data are presented as Mean±SD. Statistical significance was determined by considering $P<0.05$.

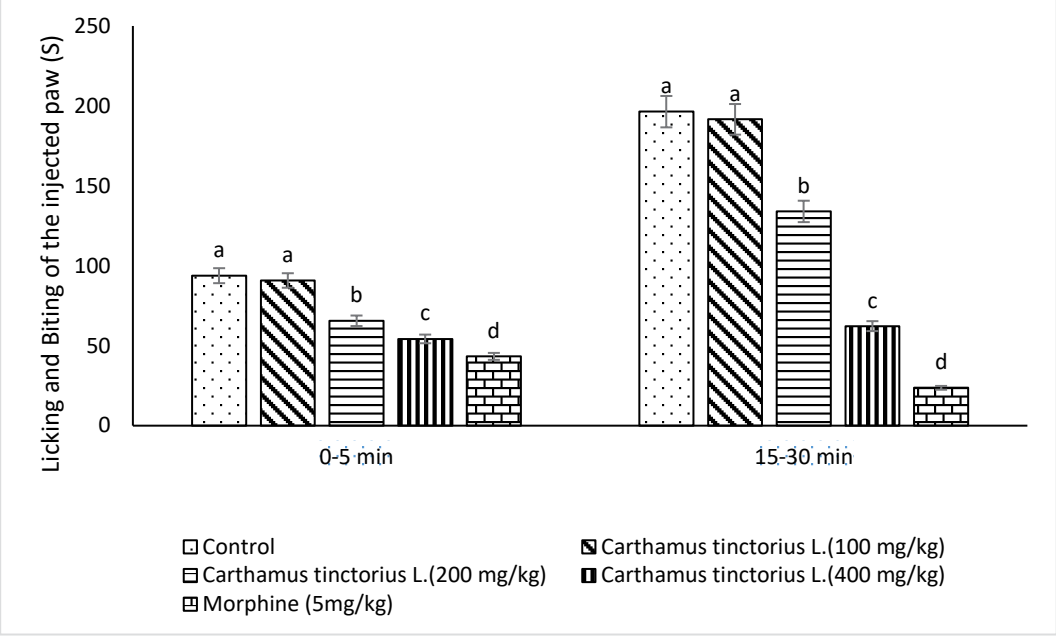

Figure 1. Effect of *C. tinctorius* L. on licking and biting time of the injected paw in male mice (n=0)

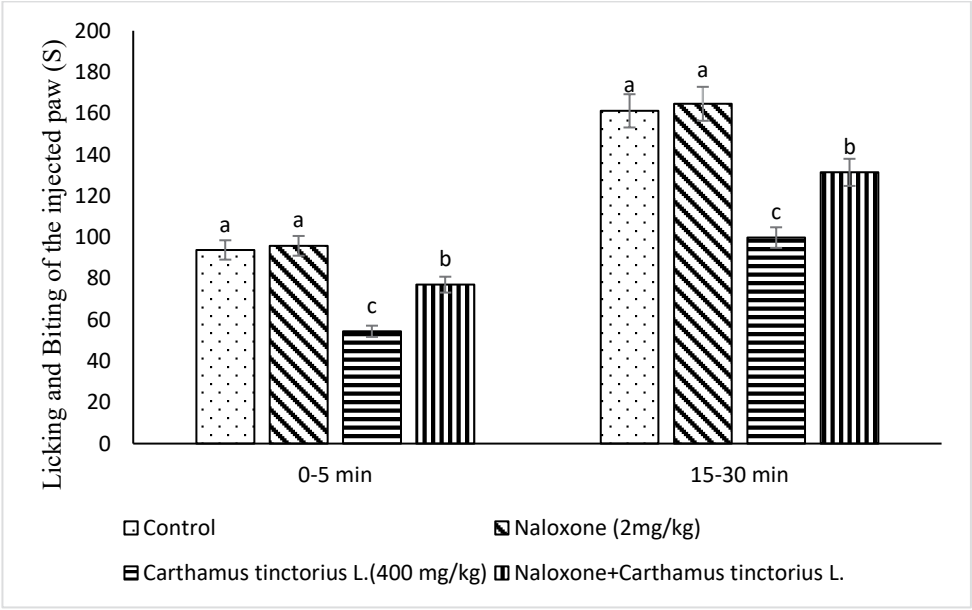

Figure 2. Effect of naloxone, *C. tinctorius* L. and their co-injection on licking and biting time of the injected paw in male mice

Naloxone: Opioid receptor antagonist.

Note: Data are expressed as the Mean±SE. Different superscripts (a-c) indicate significant differences between groups (P<0.05).

Results

By the results presented in Figure 1, the administration of morphine resulted in a reduction in the duration of licking and biting, indicating a pain response in the formalin test (P<0.05). Additionally, *C. tinctorius* L. exhibited a decrease in pain response compared to the control animals (P<0.05).

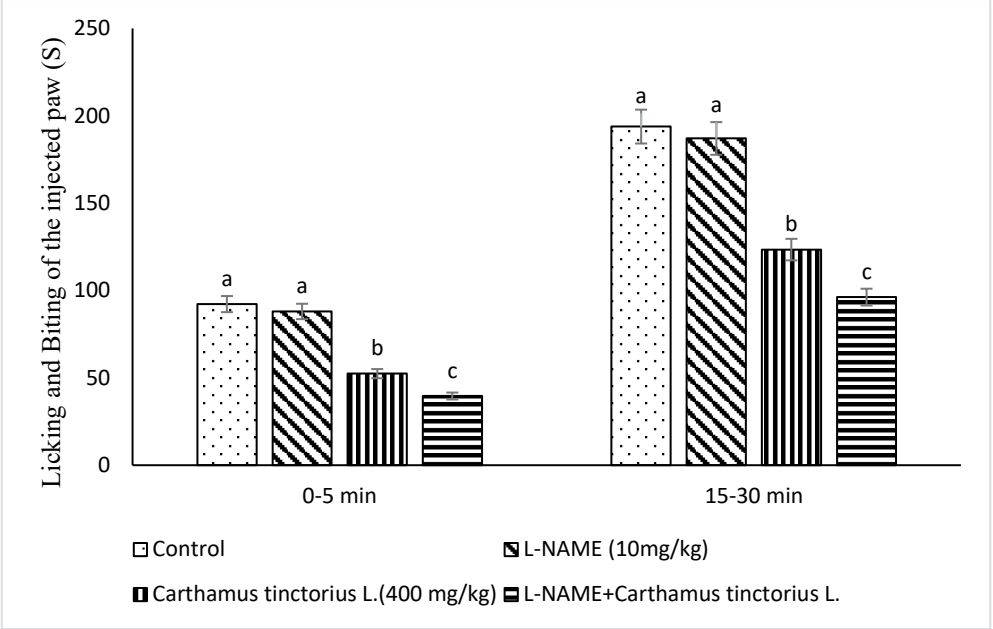

Figure 3. Effect of L-Name, C. *tinctorius* L. and their co-injection on licking and biting time of the injected paw in male mice

L-Name: Nitric oxide inhibitor.

Note: Data are expressed as the Mean±SE. Different superscripts (a-c) indicate significant differences between groups (P<0.05).

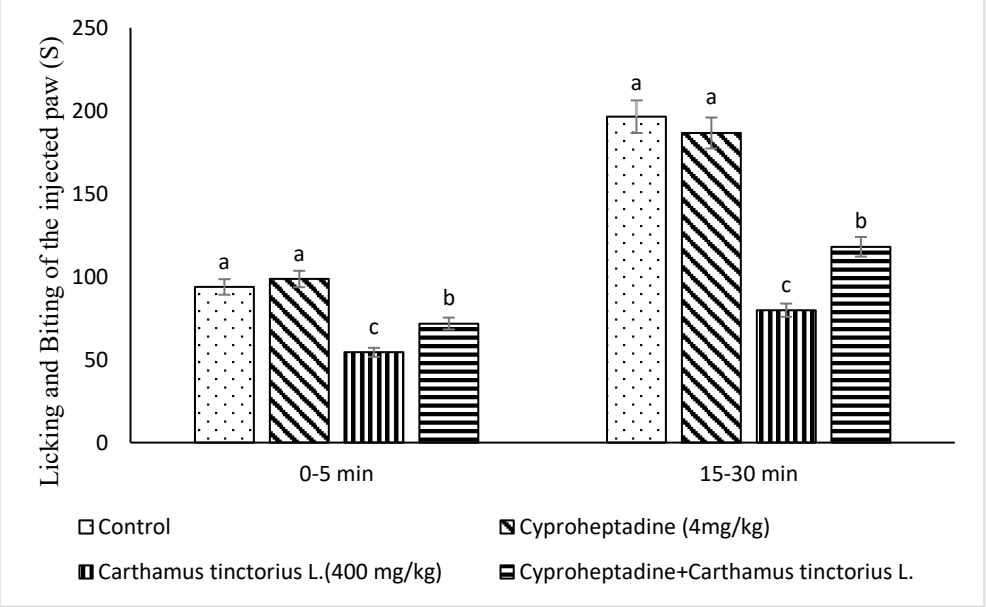

Figure 4. Effect of cyproheptadine, *C. tinctorius* L. and their co-injection on licking and biting time of the injected paw in male mice

Cyproheptadine: Serotonergic receptor antagonist.

Note: Data are expressed as the Mean±SE. Different superscripts (a-c) indicate significant differences between groups (P<0.05).

Data are expressed as the Mean±SE. Different superscripts (a-d) indicate significant differences between groups (P<0.05).

The results shown in Figure 2 indicate that naloxone (2 mg/kg) did not elicit an antinociceptive response (P>0.05). In contrast, administration of *C. tinctorius* L. (400 mg/kg) effectively inhibited the pain response in the injected

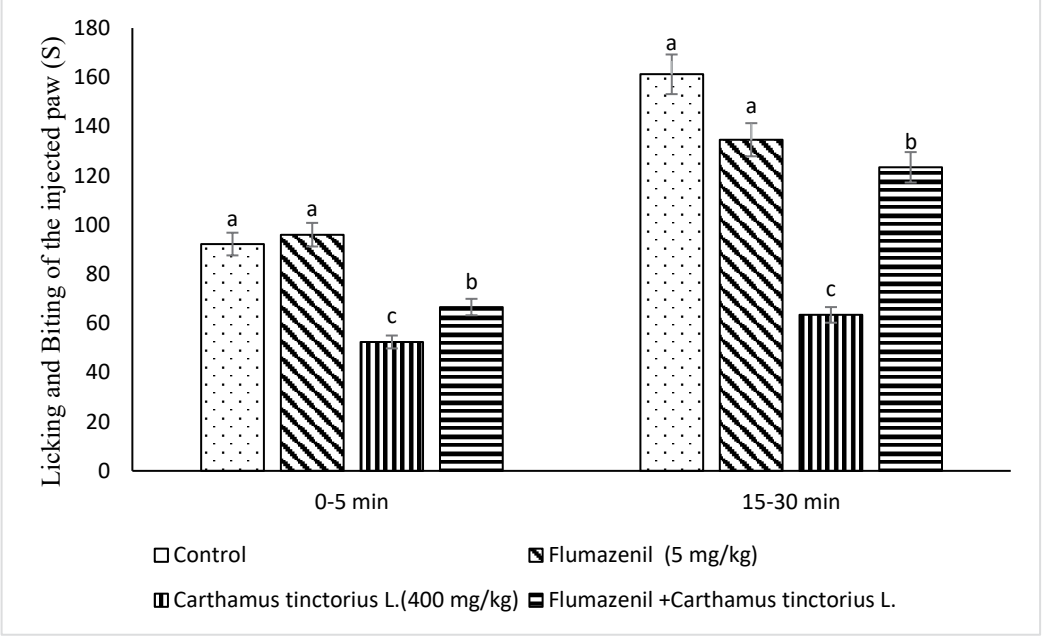

Figure 5. Effect of flumazenil, *C. tinctorius* L. and their co-injection on licking and biting time of the injected paw in male mice

Flumazenil: GABAergic receptor antagonist.

Note: Data are expressed as the Mean±SE. Different superscripts (a-c) indicate significant differences between groups (P<0.05).

paw in comparison to the control mice (P<0.05). Furthermore, the injection of naloxone combined with *C. tinctorius* L. reduced the pain response during the formalin test (P<0.05). These results suggested that the opioidergic system mediated the observed effects of *C. tinctorius* L.

According to the data presented in Figure 3, administration of L-NAME (10 mg/kg) did not induce antinociception in the formalin test (P>0.05). However, *C. tinctorius* L. (400 mg/kg) effectively inhibited the pain response in the injected paw compared to the control mice (P<0.05). The injection of L-NAME combined with *C. tinctorius* L. led to decreased pain response during the formalin test (P<0.05). The observed effects of *C. tinctorius* L. are mediated by nitrergic systems.

As depicted in Figure 4, administration of *C. tinctorius* L. (400 mg/kg) effectively inhibited pain response in the injected paw in comparison to the control mice (P<0.05). Conversely, the administration of cyproheptadine (4 mg/kg) did not exhibit any antinociceptive effect (P>0.05). However, when cyproheptadine was administered combined with *C. tinctorius* L., pain response was reduced during the formalin test (P<0.05). The observed effects of *C. tinctorius* L. are mediated by the serotonergic system.

The results presented in Figure 5 demonstrate that the administration of flumazenil (5 mg/kg) did not elicit an antinociceptive response (P>0.05). Conversely, *C. tinctorius* L. (400 mg/kg) effectively inhibited the pain response in the injected paw compared to the control mice (P<0.05). Furthermore, the injection of flumazenil combined with *C. tinctorius* L. reduced the pain response during the formalin test (P<0.05). These results suggest that the GABAergic system mediates the observed effects of *C. tinctorius* L.

Discussion

By these results, *C. tinctorius* L. exhibited a decrease in pain response. Injection of naloxone in combination with *C. tinctorius* L. reduced the pain response during the formalin test. Injection of L-Name combined with *C. tinctorius* L. led increased pain response during the formalin test. Cyproheptadine was administered in combination with *C. tinctorius* L. and a reduction in pain response was observed. Injection of flumazenil in combination with *C. tinctorius* L. reduced the pain response. Safflower seeds have long been utilized as a traditional herbal remedy and have gained widespread usage in producing edible oils on a global scale (Farzaneh et al., 2023). Numerous studies have reported safflower seed extracts exhibit diverse biological activities, including their ability to protect bone health, inhibit fat cell formation and exert antioxidant effects. Moreover, these extracts contain various phenolic compounds with antioxidant properties (Kim et al., 2019). Previous research has successfully isolated serotonin derivatives, such as N-(p-coumaroyl) serotonin and N-(feruloyl) serotonin, as well as flavonoids, such as luteolin, kaempferol, quercetin hydrate, and lignin, from safflower seed extracts. These phenolic compounds have demonstrated significant antioxidant, anti-adipogenic, and renal protective effects. In the current study, we have also identified three active compounds in the safflower seed extract, namely serotonin and its derivatives, N-(p-coumaroyl) serotonin and N-(feruloyl) serotonin (Park et al., 2019). Previous studies have indicated that N-feruloyl serotonin and N-(p-coumaroyl) serotonin play protective roles in preventing neuronal damage in both in vitro and in vivo conditions. Serotonin, a biologically active amine, is a neurotransmitter and a hormone. Furthermore, it acts as an antioxidant by neutralizing reactive oxygen species (Takao et al., 2017).

Kim et al. (2019) conducted a study that examined the inhibitory impact of *C. tinctorius* L. on nitric oxide (NO) production in HaCaT cells stimulated with lipopolysaccharides (LPS). The results indicated that the ethanol extract of *C. tinctorius* L. effectively hindered the LPS-stimulated NO production in HaCaT cells and reduced the messenger ribonucleic acid (mRNA) and protein expressions of inducible NO synthase (iNOS). HaCaT cells induced by LPS generate a swift inflammatory response that can release pro-inflammatory cytokines (IL-6 and IL-1) and inflammatory mediators (iNOS). Thus, the anti-nociceptive role of *C. tinctorius* L. is mediated via this mechanism. However, further research is needed to determine the accuracy of these findings. NO has a crucial nociceptive function in the central and peripheral nervous systems. Furthermore, it augments the generation or release of reactive oxygen species in cases of inflammatory pain (Ping et al., 2018). Naturally occurring compounds exhibit antioxidant and anti-inflammatory characteristics, effectively mitigating oxidative stress and neuropathic pain. By this, Dadpisheh et al. have shown that troxerutin enhances the levels of catalase, paraoxonase 1, glutathione peroxidase and NO in sciatic nerve ischemia-reperfusion injury cases. Oxidative stress, which results from an imbalance between the production of oxygen free radicals and the capacity for antioxidant action, impairs biological macromolecules and disrupts normal metabolism and physiology (Patil et al., 2024). Endogenous antioxidants exert their influence by scavenging oxygen free radicals, thereby delaying or

inhibiting cellular damage, primarily through their ability to scavenge free radicals. Additionally, troxerutin effectively scavenges reactive oxygen species and reduces nuclear factor kappa B (NF-κB) expression in diabetic rats and patients afflicted by cardiovascular diseases (Najafi et al., 2018).

Conclusion

In conclusion, these results suggest that the anti-nociceptive activity of *C. tinctorius* L. is mediated via the opioidergic, nitrergic, serotonergic and GABAergic systems in mice.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Supervisor: Shahin Hassanpour; Data collection: Elaheh Tadayon.

Conflict of interest

The authors declared no conflict of interest.

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