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Anti-nociceptive activity of the Safflower *(Carthamus tinctorius L.)* in mice

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Abstract

Background: pain serves as a traditional indication of the inflammatory reaction, resulting in the manifestation of allodynia or hyperalgesia and *Carthamus tinctorius L.* has demonstrated various biological activities.

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

Methods: A total of 105 adult male NMRI mice, were assigned at random to participate in five separate experiments, with each experiment consisting of four groups. In the initial trial, mice were subjected to the administration of saline, an extract derived extract of *Carthamus tinctorius L.* (100, 200 and 400mg/kg) and morphine at a dosage of 5 mg/kg. In the second trial, the subjects were treated with saline, naloxone (2mg/kg), extract of *Carthamus tinctorius L.* (400mg/kg), and combination of an extract of *Carthamus tinctorius L.* and naloxone. In trial 3-5, L-NAME (10mg/kg), cyproheptadine (4mg/kg) and flumazenil (5mg/kg) were used instead of naloxone. Then formalin was injected and paw licking time (pain sense) was recorded.

Results: In accordance with the findings *Carthamus tinctorius L.* exhibited a decrease in pain response when compared to the control animals ($P<0.05$). Injection of naloxone in combination with *Carthamus tinctorius L.* resulted in a reduction in pain response during the formalin test ($P<0.05$). Injection of L-NAME in combination with *Carthamus tinctorius L.* led to an increase in pain response during the formalin test ($P<0.05$). Cyproheptadine was administered in combination with *Carthamus tinctorius L.*, a reduction in pain response was observed during the formalin test ($P<0.05$). injection of flumazenil in combination with *Carthamus tinctorius L.* resulted in a reduction in pain response during the formalin test ($P<0.05$).

Conclusion: These results suggested antinociceptive activity of the *Carthamus tinctorius L.* mediates via opioidergic, nitrergic, serotonergic and GABAergic system in mice.

Keywords: Anti-nociceptive, Safflower, nitrergic, serotonergic, GABAergic

1. Introduction

pain serves as a traditional indication of the 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). The process of inflammation triggers the activation of peripheral nerve fibers and brings about alterations in local blood circulation and the permeability of blood vessels (Farahani *et al.,* 2021). Moreover, immune cells that are activated during inflammation release pro-algesic 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, continues to be an unfulfilled medical necessity in recent years. While pharmacotherapy centered around the usage

of opioids still 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 the 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 in order to surmount the existing 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 associated with the prolonged usage of synthetic medications for the treatment of painful conditions and inflammation, numerous studies have explored various plant extracts and their active compounds in order to evaluate their potential for exerting anti-nociceptive 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 Carthamus tinctorius L., is highly valued for its nutritional composition. It comprises approximately 70% polyunsaturated fatty acid, specifically linoleic acid, 10% monounsaturated oleic acid, and minimal amounts of stearic acid (Delshad *et al.*, 2018). *Carthamus 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 the florets of *Carthamus tinctorius L.* (kim et al. 2023). In Iranian folk medicine, safflower has been employed for the treatment of cerebrovascular disease and heart disease (Delshad *et al.,* 2018). Moreover, Safflower exhibits notable purgative, analgesic, and antipyretic properties, making it beneficial for patients with poisoning (Gautam *et al.,* 2014). Several pieces of evidence have illustrated that *Carthamus tinctorius L.* exhibits an anti-inflammatory influence (Delshad *et al.,* 2018). Among a multitude of pain models, the formalin-induced pain is considered to be a pain caused by inflammation (Hong *et al.,* 2020). Based on literature, there is no report on anti-nociceptive activity of the *Carthamus tinctorius L.* in mice. Thus, this study aimed to determine anti-nociceptive activity of the *Carthamus tinctorius L.* using formalin-test in mice.

2. Material and Methods

2.1. Animals

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

2.2. Extraction and chemicals

Carthamus tinctorius L. flowers were fully dried at room temperature, away from sunlight, powdered using mechanical mill. Subsequently, the extraction process was carried out employing a maceration method with a 70% methanolic solvent. This extraction procedure was replicated thrice, with each iteration lasting for a duration of 24 hours. The obtained extracts were thoroughly desiccated utilizing a vacuum-assisted rotary evaporator, ensuring that the temperatures did not exceed 45°C. The resultant extracts were then preserved in a refrigerated environment until they were ready to be utilized (Hosseinzadeh et al. 2009). Morphine, Naloxone, L-NAME (nitric oxide inhibitor), cyproheptadine (serotonergic receptor antagonist) and flumazenil (GABAergic receptor antagonist) purchased from Sigma (St. Louis, MO, USA). Also, ethanol and formalin were purchased from Merck (Darmstadt, Germany). Drugs were first dissolved in saline and then were intraperitoneally injected (volume of 0.5 mL). The dosage of the drugs was obtained from previous reports (Wang *et al.,* 2014; Hassanpour *et al.,* 2020; Kim *et al.,* 2023).

2.3. Formalin test

In the initial trial, mice were subjected to the administration of saline, an extract derived extract of *Carthamus tinctorius L.* at a dosage of 100 mg/kg, an extract derived from *Carthamus tinctorius L.* at a dosage of 200 mg/kg, an extract of *Carthamus tinctorius L.* at a dosage of 400 mg/kg, and morphine at a dosage of 5 mg/kg. Subsequently, after a period of thirty minutes, a 1% formalin solution, measuring 50 µL, was injected into the plantar surface of the right paw (Figure 1). In the second trial, the subjects were treated with saline, naloxone at a dosage of 2 mg/kg, an extract derived from the plant *Carthamus tinctorius L.* at a dosage of 400 mg/kg, and a combination of an extract of *Carthamus tinctorius L.* and naloxone (Figure 2). In cases where

two injections were performed, the subjects primarily received the antagonist, followed by the administration of *Carthamus tinctorius L.* after a period of 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 at a dosage of 10 mg/kg, an extract of *Carthamus tinctorius L.* at a dosage of 400 mg/kg, and a combination of an extract of *Carthamus tinctorius L.* and L-NAME (Figure 3). In the fourth trial, the mice were intraperitoneally injected with saline, cyproheptadine at a dosage of 4 mg/kg, an extract of *Carthamus tinctorius L.* at a dosage of 400 mg/kg, and a combination of an extract of *Carthamus tinctorius L.* and cyproheptadine (Figure 4). In the fifth trial, the mice were intraperitoneally injected with saline, flumazenil at a dosage of 5 mg/kg, an extract of *Carthamus tinctorius L.* at a dosage of 400 mg/kg, and a combination of an extract of *Carthamus tinctorius L.* and flumazenil (Figure 5). The analgesic effect of *Carthamus tinctorius L.* in was assessed utilizing the formalin test as described by Dubuisson and Dennis (1977), with certain modifications. The procedure involved injecting 20 µl of 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 duration of time spent licking and/or biting the injected hind paw was recorded in 5-minute intervals over a 30-minute observation period. The formalin test comprises of 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), subsequent to the formalin injection (Mota *et al.,* 2011).

2.4. Statistical analysis

Data were subjected to analysis SPSS version 22. The analysis employed One-way Analysis of Variance (ANOVA) followed by Tukey post-hoc test. All data were presented as mean ± standard deviation (SD). Statistical significance was determined by considering P-values less than 0.05.

3. Results

In accordance with the findings presented in figure 1, the administration of morphine resulted in a reduction in the duration of licking and biting, which are indicative of pain response, in the formalin test ($P < 0.05$). Additionally, *Carthamus tinctorius L.* exhibited a decrease in pain response when compared to the control animals ($P < 0.05$).

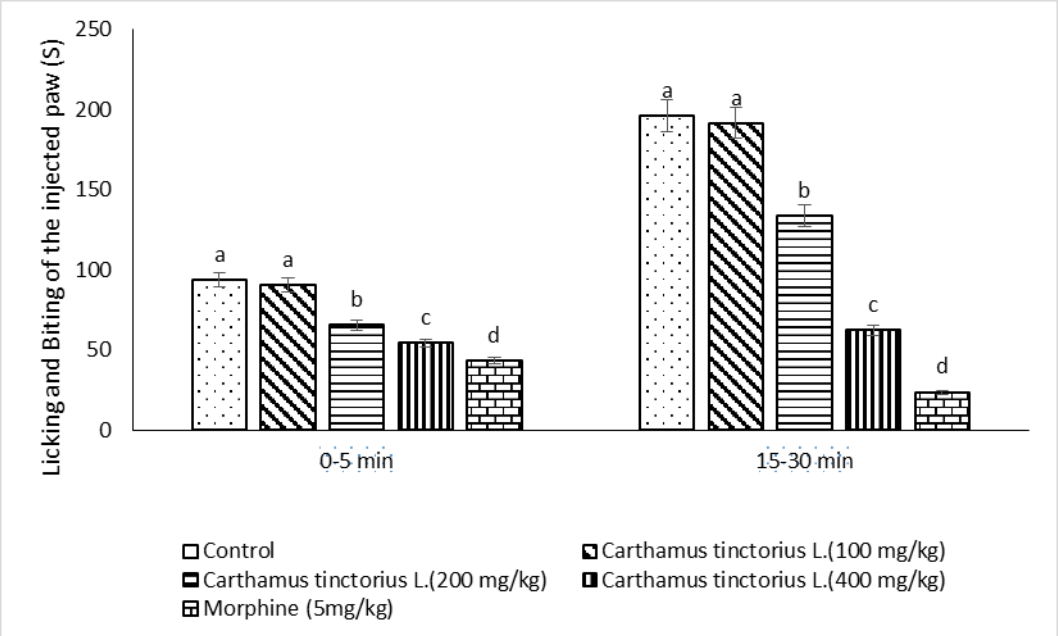

Figure 1. Effect of *Carthamus tinctorius L.* on Licking and Biting Time of the Injected Paw in Male Mice (n = 50). Data are expressed as mean ± SE. Different superscripts (a-d) indicate significant differences between groups (P < 0.05).

The results depicted in figure 2 indicate that naloxone (2 mg/kg) did not elicit an anti-nociceptive response (P >0.05). On the other hand, the administration of *Carthamus tinctorius L.* (400 mg/kg) effectively inhibited pain response in the injected paw in comparison to the control mice (P <0.05). Furthermore, the injection of naloxone in combination with *Carthamus tinctorius L.* resulted in a reduction in pain response during the formalin test (P <0.05). The findings suggest that the observed effects of *Carthamus tinctorius L.* were mediated by the opioidergic system.

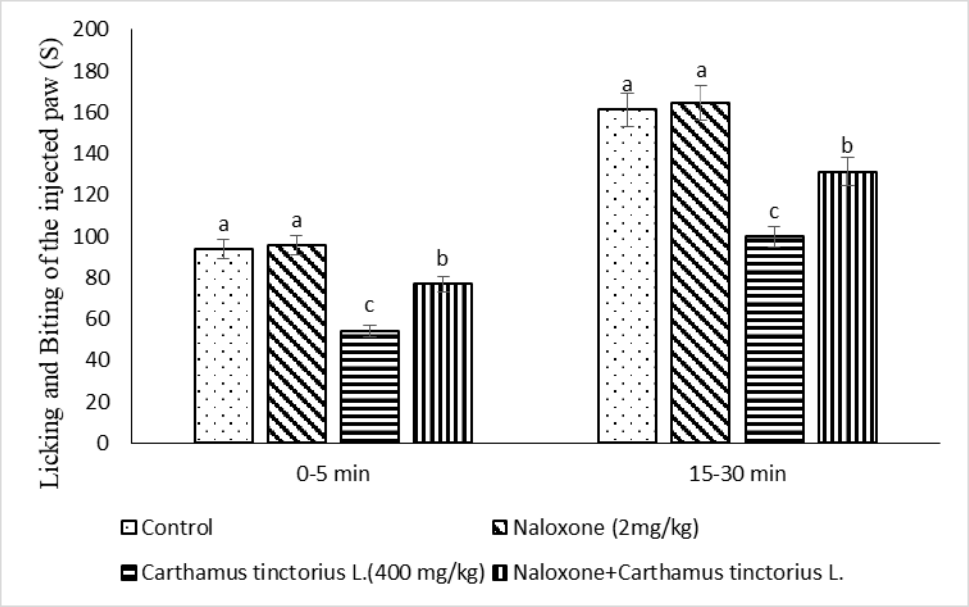

Figure 2. Effect of Naloxone, *Carthamus tinctorius L.*, and their Co-injection on Licking and Biting Time of the Injected Paw in Male Mice. Naloxone: opioid receptor antagonist. Data are expressed as mean ± SE. Different superscripts (a-c) indicate significant differences between groups ($P < 0.05$).

According to the data presented in figure 3, the administration of L-NAME (10 mg/kg) did not induce anti-nociception in the formalin test ($P > 0.05$). However, *Carthamus tinctorius L.* (400 mg/kg) effectively inhibited pain response in the injected paw when compared to the control mice ($P < 0.05$). Interestingly, the injection of L-NAME in combination with *Carthamus tinctorius L.* led to an decrease in pain response during the formalin test ($P < 0.05$). It appears that the observed effects of *Carthamus tinctorius L.* were mediated by nitrergic systems.

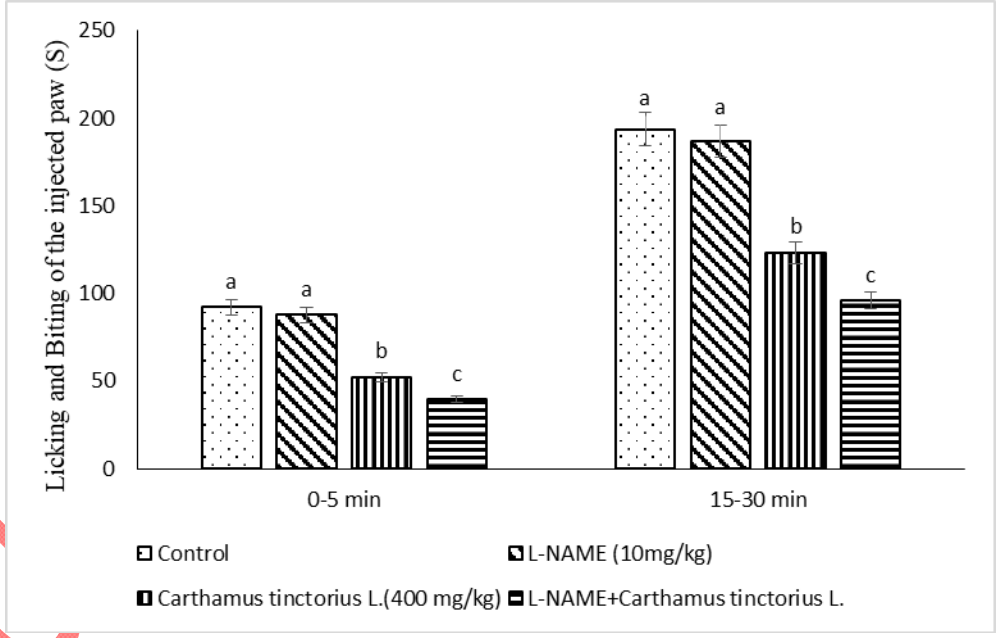

Figure 3. Effect of L-NAME, *Carthamus tinctorius L.*, and their Co-injection on Licking and Biting Time of the Injected Paw in Male Mice. L-NAME: nitric oxide inhibitor. Data are expressed as mean ± SE. Different superscripts (a-c) indicate significant differences between groups ($P < 0.05$).

As depicted in figure 4, the administration of *Carthamus 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 in combination with *Carthamus tinctorius L.*, a reduction in pain response was observed during the formalin test ($P < 0.05$). It is evident that the observed effects of *Carthamus tinctorius L.* were mediated by the serotonergic system.

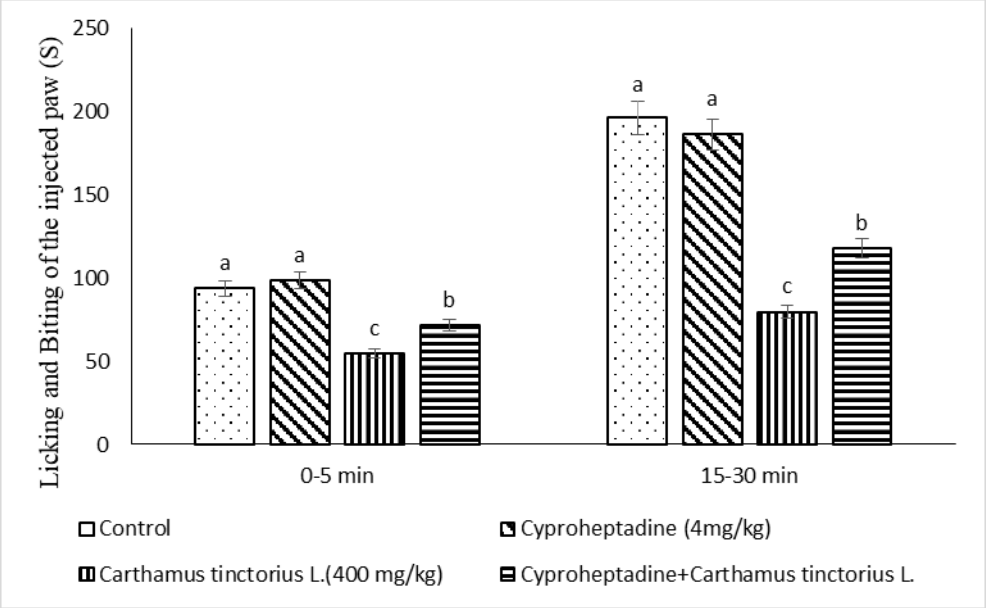

Figure 4. Effect of cyproheptadine, *Carthamus tinctorius L.*, and their Co-injection on Licking and Biting Time of the Injected Paw in Male Mice. cyproheptadine: serotonergic receptor antagonist. Data are expressed as mean ± SE. Different superscripts (a-c) indicate significant differences between groups ($P < 0.05$).

The findings presented in figure 5 demonstrate that the administration of flumazenil (5 mg/kg) did not elicit an anti-nociceptive response ($P > 0.05$). Conversely, *Carthamus tinctorius L.* (400 mg/kg) effectively inhibited pain response in the injected paw in comparison to the control mice ($P < 0.05$). Furthermore, the injection of flumazenil in combination with Carthamus tinctorius L. resulted in a reduction in pain response during the formalin test ($P < 0.05$). These results suggest that the observed effects of *Carthamus tinctorius L.* were mediated by the GABAergic system.

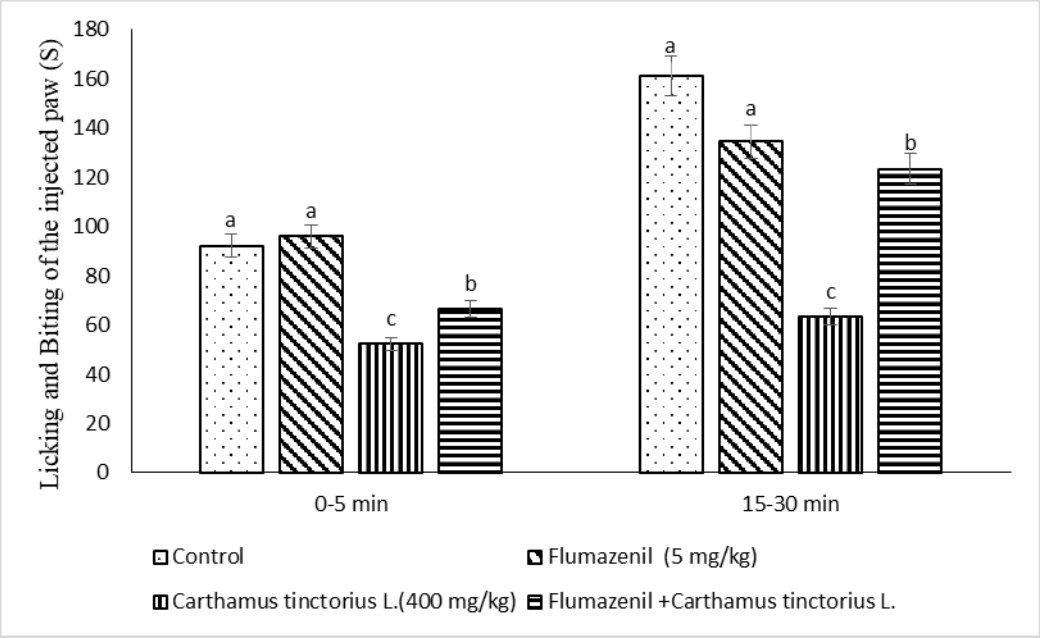

Figure 5. Effect of flumazenil, *Carthamus tinctorius L.*, and their Co-injection on Licking and Biting Time of the Injected Paw in Male Mice. flumazenil: GABAergic receptor antagonist. Data are expressed as mean ± SE. Different superscripts (a-c) indicate significant differences between groups ($P < 0.05$).

4. Discussion

In accordance with the findings *Carthamus tinctorius L.* exhibited a decrease in pain response. Injection of naloxone in combination with *Carthamus tinctorius L.* resulted in a reduction in pain response during the formalin test. Injection of L-NAME in combination with *Carthamus tinctorius L.* led to an increase in pain response during the formalin test. Cyproheptadine was administered in combination with *Carthamus tinctorius L.*, a reduction in pain response was observed. injection of flumazenil in combination with *Carthamus tinctorius L.* resulted in a reduction in pain response. Safflower seeds have long been utilized as a traditional herbal remedy and have gained widespread usage in the production of edible oils on a global scale (Farzaneh *et al.,* 2023). Numerous studies have reported the diverse biological activities exhibited by safflower seed extracts, including their ability to protect bone health, inhibit the formation of fat cells, and exert antioxidant effects. Moreover, these extracts contain a variety of phenolic compounds that possess 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 like luteolin, kaempferol, and quercetin hydrate, and lignin from safflower seed extracts. These phenolic compounds have demonstrated significant antioxidant, anti-adipogenic, and renal protective effects. In our current investigation, 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 a protective role in preventing neuronal damage under both in vitro and in vivo conditions. Serotonin, a biologically active amine, serves as a neurotransmitter and hormone. Furthermore, it acts as an antioxidant by neutralizing reactive oxygen species (ROS) (Takao *et al.*, 2017).

Kim *et al.,* (2023) conducted a study to examine the inhibitory impact of *Carthamus tinctorius L.* on the production of NO in HaCaT cells when stimulated with LPS. The findings indicated that the ethanol extract of *Carthamus tinctorius L.* effectively hindered the LPS-stimulated NO production in HaCaT cells and reduced the mRNA and protein expressions of iNOS. HaCaT cells induced by LPS generate a swift inflammatory response that can release pro-inflammatory cytokines (IL-6 and IL-1) along with inflammatory mediators (iNOS). Thus, we think maybe anti-nociceptive role of the *Carthamus tinctorius L.* mediates via this mechanism. However, more research needs to determine accuracy of the findings. Nitric oxide possesses a crucial nociceptive function in both the central and peripheral nervous systems. Furthermore, it augments the generation or release of reactive oxygen species in instances of inflammatory pain (Ping *et al.,* 2018). A naturally occurring compound, it exhibits antioxidant and anti-inflammatory characteristics, effectively mitigating oxidative stress and neuropathic pain. In accordance with this matter, Dadpisheh *et al.,* (2020) have delineated that troxerutin enhances the levels of catalase, paraoxonase 1, glutathione peroxidase, and nitric oxide in cases of sciatic nerve ischemia-reperfusion injury. Oxidative stress, which ensues from an imbalance between the production of oxygen free radicals and the capacity for antioxidant action, impairs the

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 NF-κB expression in diabetic rats or patients afflicted by cardiovascular diseases (Najafi *et al.*, 2018).

5. Conclusions

In conclusion, these results suggested anti-nociceptive activity of the *Carthamus tinctorius L.* mediates via opioidergic, nitrergic, serotonergic and GABAergic system in mice.

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اثرات ضد دردری گلرنگ در موش کوچک آزمایشگاهی

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چکیده

زمینه: درد به عنوان یک نشانه سنتی از واکنش التهابی عمل می کند که منجر به تظاهرات آلودینیا یا پردردی می شود و گیاه گلرنگ فعالیت های بیولوژیکی مختلفی را نشان داده است.

هدف: این مطالعه با هدف تعیین فعالیت ضددردی گیاه گلرنگ در موش کوچک آزمایشگاهی انجام شد.

روش کار: در مجموع 105 موش نر بالغ NMRI به طور تصادفی برای شرکت در پنج آزمایش جداگانه، که هر آزمایش شامل چهار گروه بود، قرار گرفتند. در آزمایش اولیه، موش‌ها تحت تجویز سالین، عصاره مشتق شده از عصاره گلرنگ (100، 200 و 400 میلی‌گرم بر کیلوگرم) و مورفین با دوز 5 میلی‌گرم بر کیلوگرم قرار گرفتند. در کارآزمایی دوم، آزمودنی ها با سالین، نالوکسان (2 میلی‌گرم بر کیلوگرم)، عصاره گلرنگ (400 میلی‌گرم بر کیلوگرم) و ترکیبی از عصاره گلرنگ و نالوکسان تحت درمان قرار گرفتند. در کارآزمایی 3-5، L-NAME (10 میلی‌گرم بر کیلوگرم)، سیپروهپتادین (4 میلی‌گرم بر کیلوگرم) و

فلومازنیل (5 میلی‌گرم بر کیلوگرم) به جای نالوکسان استفاده شد. سپس فرمالین تزریق شد و زمان لیسیدن پنجه (حس درد) ثبت شد.

یافته ها: مطابق با یافته ها عصاره گلرنگ موجب کاهش در پاسخ درد در مقایسه با حیوانات کنترل شد ($P < 0.05$). تزریق نالوکسان در ترکیب با عصاره گلرنگ منجربه کاهش پاسخ درد در طی تست فرمالین شد ($P < 0.05$). تزریق L-NAME در ترکیب با عصاره گلرنگ منجربه افزایش پاسخ درد در طی تست فرمالین شد ($P < 0.05$). سیپروهپتادین در ترکیب با عصاره گلرنگ تجویز شد، کاهش در پاسخ درد در طول تست فرمالین مشاهده شد ($P < 0.05$). تزریق فلومازنیل در ترکیب با عصاره گلرنگ منجر به کاهش پاسخ درد در طی تست فرمالین شد ($P < 0.05$).

نتیجه گیری: این نتایج نشان می‌دهد که فعالیت ضددردی عصاره گلرنگ از طریق سیستم اوپیوئیدرژیک، نیتررژیک، سروتونرژیک و گاباارژیک در موش واسطه‌گری می‌شود.

کلمات کلیدی: ضددردی، گلرنگ، نیتررژیک، سروتونرژیک، گاباارژیک