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Review Article

Nociception and herbal plants: A review on the most important herbal plants effective on chronic pain

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Abstract

Chronic pain can be periodic, persistent, or even a combination of both. Unlike acute pain, chronic pain is not usually useful, reduces the quality of life and functional abilities and also weakens mental health, interpersonal relationships, and financial status, leading to changes in appetite, sleep disorders, psychomotor retardation, tiredness and depression. Human being has always faced various kinds of pain during life and sought to relieve his pain. Pain is a sign of a disease that acts as a warning mechanism and informs of a tissue injury. In this regard, the analgesic effects of many medicinal plants have also been studied. Therefore, in this review study, indigenous medicinal plants with anti-chronic pain effects were reported. Information to conduct this review was obtained using the keywords chronic pain, herbal drug, Iran, medicinal plants, extracts and essential oils to retrieve articles indexed in databases such as Scopus, SID, Magiran, Google Scholar and other Persian databases. The related articles were reviewed for plants serving as chronic pain killers. After reviewing the literature, it was found that *Solanum melongena*, *Hyoscyamus niger*, *Phoenix dactylifera*, *Cinnamomum zeylanicum*, *Artemisia sieberi*, *Crocus sativus*, *Carum copticum*, *Euphorbia helioscopia*, *Hypericum perforatum*, *Cucurbita maxima*, *Passiflora caerulea*, *Rosa damascena*, *Tanacetum parthenium*, *Allium jesdianum* and *Pistacia atlantica* among indigenous medicinal plants with analgesic effect.

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Introduction

Pain is an unpleasant feeling caused by tissue injury, and if not treated, it can prevent the daily activities of life (1, 2). Pain is a physiological response to an annoying trigger, which everyone

has experienced in his/her personal life. Most people complain of pain in their daily lives or in hospitals, so that pain is the main reason for referral to the emergency (3-5). Chronic pain is associated with other topics such as slow burning

pain, vague pain, pulsatile pain and nausea pain. Chronic pain is felt after one second or more and then slowly intensifies in a few seconds, and sometimes even up to one minute later. The origin of chronic pain can be neurogenic, nociceptive, psychotic or unknown. It can also be periodic, persistent or even a combination of both. In contrary to acute pain, chronic pain is not usually useful, reduces the quality of life and functional abilities and also weakens mental health, interpersonal relationships and financial status. In addition, chronic pain can lead to changes in appetite, sleep disorders, psychomotor retardation, mood disorder, fear of the community, and depression (6, 7). Pain is considered a symptom of a disease that acts as a warning mechanism and informs of a tissue injury (8). Regardless of the origin of the disease, today pain is the most common discomfort of human communities, especially in industrialized countries and developing countries (9, 10). Pain can be caused by damage to tissues by harmful stimuli such as chemical, electrical, thermal, and mechanical stimuli, and can be acute and chronic (11). Throughout his life, man has always faced various kinds of pain and has sought to relieve his pain. After the synthesis of chemical analgesic drugs, their entry into the market and their extensive use to relieve pain, their side effects also appeared. For example, opioids also appear to cause nausea, respiratory weakness, constipation, and in case of being taken in the long term, addiction (12). For the treatment of pain in the recent century, non-steroidal anti-inflammatory drugs and opioids have been extensively used that lead to side effects (13, 14). The use of medicinal plants to relieve pain has a long history in the world of medicine and in Iran, and given that the use of herbal drugs at the conventional doses has lesser risks than synthetic drugs, the attention of researchers has been drawn to the use of medicinal plants. One of the earliest methods of coping with diseases is the traditional use of medicinal plants. Many plant herbs are herbs that are always available and are easy to use and consuming, including ginger, turmeric, peppermint, spicy pepper and a number of other herbs. These have been used for pain relief in Iran since ancient times. Plants and materials extracted from them are used to treat various diseases such as infectious, non-infectious and chronic diseases in humans (15-21). Today, due to the lower side effects of medicinal plants, the tendency to use them is increasing. In this regard, the analgesic effects of many medicinal plants have also been studied (22, 23). In this review study, indigenous medicinal plants with anti-chronic pain effects were reported.

Methodology

Information to conduct this review was obtained using the keywords chronic pain, herbal drug, Iran, medicinal plants, extracts and essential oils

to retrieve articles indexed in databases such as Scopus, Google Scholar, SID, Magiran and other Persian databases. The related articles were reviewed for plants serving as analgesic.

Results

After reviewing the literature, it was found that *Solanum melongena* L., *Hyoscyamus niger* L., *Phoenix dactylifera* L., *Cinnamomum zeylanicum* J.Presl, *Artemisia sieberi* Besser, *Crocus sativus* L., *Carum copticum* (L.) C. B. Clarke, *Euphorbia helioscopia* L., *Hypericum perforatum* L., *Cucurbita maxima* Duchesne, *Passiflora caerulea* L., *Rosa damascena* Mill., *Tanacetum parthenium* (L.) Sch. Bip., *Allium jesdianum* Boiss. & Buhse and *Pistacia atlantica* Desf., among indigenous medicinal plants with analgesic effect were the most important.

Solanum melongena L.

The results of a study that investigated the anti-chronic pain effect of hydroalcoholic extract of *S. melongena* in mouse model, showed that the extract of *S. melongena* at a dose of 1000 mg/kg of formalin test reduced the pain of chronic phase, with a significant difference between 20 min and 40 min intervals compared to the control group (24).

Hyoscyamus niger L.

Statistical analysis of the data of a study showed that injection of hydroalcoholic extract of *Hyoscyamus niger* seeds in studied doses (500, 1000 and 2000 mg/kg) decreased the pain due to formalin test in male rats compared to the control group (25).

Phoenix dactylifera L.

The results of one study showed that the long-term effects of aqueous extract of 10% *P. dactylifera* in the chronic phase of formalin test in male rat model showed significant analgesic effects compared to the control group (26). The results of formalin test in the study of the analgesic effect of hydroalcoholic extract of *P. dactylifera* in the mouse model showed that the mean pain severity in the formalin test in the control group was 0.0599 ± 1.665 and at 2, 20 and 200 mg of the extract 0.660 ± 1.079 , 0.0822 ± 0.9192 and 0.0658 ± 0.3842 , respectively (32).

Cinnamomum zeylanicum J.Presl

The results of a study investigating the effect of cinnamon extract on the chronic pain of large mice using formalin test showed that this extract reduced the second stage of pain (chronic pain) at a dose of 50 mg/kg significantly compared to the control group. The results of that study confirmed the chronic analgesic effect of high-dose cinnamon in formalin test, and it seemed that this effect was due to the anti-inflammatory effect of the plant (27).

***Artemisia sieberi* Besser**

The results of one study on the effect of hydroalcoholic extract of *A. sieberi* on mice showed that the analgesic effect of the extract in chronic pain phase was more pronounced, with analgesic effect of 4000 mg/kg of *A. sieberi* being higher than morphine 2 mg/kg (28).

***Crocus sativus* L.**

The results of one study on the anti-chronic pain effect of aqueous extract of *Crocus sativus* showed that an extract of *C. sativus* flower with 10, 50 and 100 mg/kg doses in laboratory mice showed analgesic effects (29).

***Carum copticum* (L.) C. B. Clarke**

The analgesic effects of alcoholic *Carum copticum* extract on chronic pain in mice with intraperitoneal injection of *C. copticum* extract (400 mg/kg) with different concentrations of morphine sulfate (1 and 2 mg/kg) showed that *Carum copticum* in the first phase had no effect on formalin-induced pain, which was considered as a type of acute pain, but its effect on the second phase of formalin-induced pain, which was a chronic pain, was significant (30).

***Euphorbia helioscopia* L.**

The results of one study on mice showed that there was a significant difference between the extract of 8 mg in the chronic pain phase compared to the control group (31).

***Hypericum perforatum* L.**

The results of one study showed that the aqueous extract of *H. perforatum* at 200, 400 and 800 mg/kg of body weight of male anesthetized rats increased in the chronic phase of formalin test, but sodium salicylate was effective only on the second phase of formalin test (33).

***Cucurbita maxima* Duchesne**

The results of one study showed that the hydroalcoholic extract of *C. maxima* at doses of 50, 100 and 200 mg/kg caused significant chronic pain in the rat compared to the control group (34).

***Passiflora caerulea* L.**

The results of one study showed that methanolic extract of *P. caerulea* at doses ranging from 80 to 300 mg/kg had significant inhibitory effects on the chronic phase response of formalin test and writhing test, although an increase was seen after the extract treatment at the time of tail jerk. This was lower than the effect induced by morphine compared to the controls (35).

***Rosa damascena* Mill.**

The results of one study showed that inhaling rose extract on the emotional and emotional dimension of pain in women and men was not effective. Meanwhile, the inhalation of *R. damascena* extract

on the sensory dimension was significantly different between men and women, but the emotional dimension was not different between women and men (36).

***Tanacetum parthenium* (L.) Sch. Bip.**

The results of one study showed that the ethanolic extract of *T. parthenium* in the experimental small mice was significantly more effective in the formalin model at a dose of 10 mg/kg body weight on the chronic phase of the pain, and a significant difference was observed between the groups of ibuprofen and distilled water (37).

***Allium jesdianum* Boiss. & Buhse**

In this study, we showed that *A. jesdianum* acts on COX activity and can be used to control prostaglandins. Our results showed that both *A. jesdianum* material and extract could inhibit COX-1 and partially inhibit COX-2, although these effects were not observed at the lowest dose. Despite the difference in COX inhibitory levels, both of the studied plant species had inhibitory effects, although showed little effect but significant (63).

***Pistacia atlantica* Desf.**

P. atlantica fruit extract 1.66 g/kg and the maximum non-fatal doses were 0.93 g/kg. The results revealed that in hot plate and tail-flick tests, *P. atlantica* fruit extract at the doses of 50, 150 and 350 mg/kg had an analgesic effect as dose-dependent, 30 minutes after administration (64).

Discussion

Pain is one of the phenomena that every human being faces during his lifetime and is a warning factor, but it is, anyway, an unpleasant feeling, and human beings have sought a way to deal with it. It can be said that the pain is a response consisting of sensory, emotional and affective constituents. The disease, inflammation, and damage to the central and peripheral nervous system cause significant changes in pain pathways such as increased irritability and gene expression. Suffering from certain pains in the long term will impose undesirable mental and psychological effects on the individual. For this reason, humans have always sought to find a solution to eliminate or reduce pain (38). It has been shown that the *Tanacetum parthenium* produces an analgesic effect via affecting inflammatory processes (38). Eggplant exerts its effect through peripheral analgesic mechanism and cholinergic pathways (39). The bang grain plant exhibits its analgesic effect with cholinergic and opioid mechanisms (40). The results of the studies show that the sweet herb has its own analgesic effects through its flavonoids and steroids (41). *Solanum melongena* has been shown to have an analgesic effect by increasing blood carbohydrates and increasing levels of β -endorphins and environmental

mechanisms (42). *Cinnamomum zeylanicum* exerts its analgesic effect by inhibiting Tumor necrosis factor and Cyclooxygenase-2, and also the production of prostaglandin as well as stimulating opioid receptors (27). The mechanisms by which *Artemisia sieberi* exerts its analgesic effects include inhibiting calcium release, blocking TRPA, inhibiting the synthesis of Nitric oxide, cytokines, and prostaglandin E2 (43). Besides, saffron has an analgesic effect by inhibiting NMDA receptors and NO synthesis (44). Studies show that the mechanisms of analgesic effect of *Hypericum perforatum* include inhibition of the Arachidonate 5-lipoxygenase and Cyclooxygenase-1 enzymes (33). Given the mechanism of the analgesic effect of the plants, it is suggested that the effect of each plant be identified and its mechanism of action be determined in order to produce an effective and potent analgesic agent.

Various compounds with their own mechanism actions might be involved in pain relieve activities of these plants, however, the role and the exact mechanism of each component should become clear. It should be noted that pain is accompanied with elevated oxidative stress and free radicals. Oxidative stress following induction of nociception results in elevation of free-radical which in turn usually imposes negative effects on pain (45). Hence, the medicinal plants presented in this article which have sufficient antioxidant activities should have acted, in part, through reducing oxidative stress. Brain is a susceptible organ to free radicals. An increase in free radicals may induce oxidative stress, because brain consumes high amount of oxygen. Also, brain contains high level of unsaturated fatty acids and low level of catalase which make this organ more susceptible to lipid peroxidation. This high level of susceptibility to oxidative stress prone the brain more than other organs to cellular damage or cell death (46). The brain oxidative stress enhances the chance of neurodegenerative disorders and pathogenesis conditions and other than pain (47, 48) increases some other psycho-neurological diseases including depression (49, 50), Alzheimer's disease (51, 52) and Parkinson's disease (53, 54). Oxidative stress also enhances the chance of non-psycho-neurological diseases such as atherosclerosis (55, 56) cardiovascular (57, 58) and diabetes mellitus diseases (59-62). As it was mentioned the pain itself is just a sign indicating other problems.

Conclusion

Hence, these plants which usually have multiple functions, other than having antinociceptive activities may also possess beneficial effects on other diseases of these patients.

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Conflicts of interest

The authors declare no conflict of interest.

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