REVIEW ARTICLE



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INTRODUCTION

Today, control and treatment of pain remains one of the most challenging issues in the medical world. IASP has defined pain as 'an unpleasant feeling or emotional experience associated with actual or potential tissue damage'.¹ In the pathophysiology of pain, there is a very complex relationship between the peripheral and central neurons from the surface of the skin to the cerebral cortex, so that it can be argued that pain is a response involving sensory, emotional and even psychological segments.²

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An overview of the important analgesic herbs in Iran

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ABSTRACT

Pain is an unpleasant feeling or emotional experience associated with actual or potential tissue damage. Even today, the control and treatment of pain remains one of the most challenging issues in medical world. An increased demand for phytotherapy and the availability of a variety of medicinal plants in Iran made it essential to study this subject. The challenges in the development of new analgesic drugs has also drawn attention towards this subject. To conduct this review, the terms medicinal plant, extracts, essential oils, traditional medicine, pain, acute pain, and chronic pain were used to retrieve relevant publications from the citation databases Magiran, SID, Google Scholar and Scopus. The subject related articles were retrieved and irrelevant articles were excluded. Based on the results, the medicinal plants such as Lavandula officinalis, Scrophularia striata, Vitis vinifera, Matricaria recutita, Solanum melongena L., Hyoscyamus niger, Achillea millefolium, Propolis, Vitex agnus castus, Malva Parviflora, Cinnamomum zeylanicum, Artemisia herba alba, Elaeagnus angustifolia. L, Anethum graveolens, Phoenix dactylifera, Hypericum perforatum L, Ziziphora cliniopodiodes, Lactuca sativa longifolia and Tanacetum parthenium etc. are among the most important analgesic plants. The medicinal plants and their active ingredients can be used to produce analgesic drugs and products. The anti-nociceptive effects of these herbs and their potential effects through inflammatory processes, inhibition of the release of arachidonic acid, synthesis of prostaglandins and its effect on the opioid system, with peripheral anti-nociceptive mechanism and cholinergic pathways, stimulation of GABA A receptors, COX-1 and 5- LO and central and environmental mechanisms. Key words: Pain; Medicinal plants; Iran

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Fifty million people at different ages suffer from pain for which over \$100 million is spent.³ Researchers have always sought to find an approach to eliminate or reduce pain, and many effective efforts have so far been made to identify the mechanisms and treatment of pain.^{4,5} Nowadays, drugs used to relieve pain and reduce inflammation are either narcotics, such as opioids, or non-narcotics; both groups have known toxic and side effects.⁶ They can lead to gastrointestinal disorders, renal lesions, respiratory failure and even dependence.^{7,8} Traditional medicine and the medicinal plants are a good source of analgesic drugs. Due to confirmed side-effects and adverse effects of chemical drugs, a shift to natural and herbal drugs has become more evident in the recent years. Many herbal sedatives are medicinal plants, that are always available and easy to use, but many people are unaware of their amazing properties. Increased demand for phytotherapy and the availability of rich sources of medicinal plants in Iran prompted us to study this phytotherapy subject. Phytotherapy is a science-based medical practice. It is distinguished from other, more traditional approaches, such as medical herbalism, which relies on an empirical appreciation of medicinal herbs and which is often linked to traditional knowledge.

METHODOLOGY

To conduct this review, the terms *medicinal plant*, *extracts*, *essential oils*, *traditional medicine*, *pain*, *acute pain*, and *chronic pain* were used to retrieve relevant publications from the citation databases *Magiran*, *SID*, *Google Scholar* and *Scopus*. In this study, a total of 28 articles were retrieved from databases. After analysis, 7 articles were removed due to repeatability, very old publication and lack of access to their full text. In the end, 21 articles were selected, which described the effects of herbs and their derivatives on pain.

RESULTS

Based on the results, the medicinal plants such as Lavandula officinalis, Scrophularia striata, Vitis vinifera, Matricaria recutita, Solanum melongena L., Hyoscyamus niger, Achillea millefolium, Propolis, Vitex agnus castus, Malva Parviflora, Cinnamomum zeylanicum, Artemisia herba alba, Elaeagnus angustifolia. L, Anethum graveolens, Phoenix dactylifera, Hypericum perforatum L, Ziziphora cliniopodiodes, Lactuca sativa longifolia and Tanacetum parthenium etc are among the most important analgesic plants. The full list of medicinal plants along with their botanical names, family names, Persian names, doses and certain explanations are given in Table 1.

DISCUSSION

Most of the people use strong painkillers when they are in pain. Some pain relief can be achieved by using anti-inflammatory drugs, but these can also produce certain side effects. The usual complications include gastritis and stomach bleeding, heart attack, kidney damage, stroke, and hormonal imbalance. Fortunately, herbal drugs have come to our aid to reduce inflammation and pain. These methods are relatively safe and very effective to reduce pain and inflammation. Medicinal plants are always available and can be conveniently used, but many people are unaware of their amazing properties. Serotonin is one of the mediators of pain and its importance in controlling pain has been frequently addressed. 5HT, 5HT, and 5HT, receptors have been identified in the spinal cord and there are different and sometimes conflicting reports about the role of these receptors in the transmission and control of pain in various pain tests. An increase in the descending activity of the serotonergic pathway is associated with analgesic effect, and decreased activity of these neurons increases the sensitivity to the agents that cause pain. One of the important factors in pain control is present in the opioid system, and opioid-induced analgesia is due to the pre-synaptic effects of C-fibers and second-degree neurons, as well as the effect on spinal interneurons. The repeated use of opioids leads to three conditions, namely, tolerance, psychological dependence and physical dependence. Medicinal plants have effects on infectious and noninfectious diseases due to active phytochemicals in them.²⁶⁻³¹ Medicinal plants produce specific medicinal effects due to active ingredients such as flavones, flavonoids, anthocyanins, tannins and other antioxidants. It is also likely that medicinal plants addressed in this study reduce pain due to these active ingredients.

For example, a lavender plant with an effect on inflammatory processes has reduced pain in the formalin test.³² The cocute plant inhibits the release of arachidonic acid and the synthesis of prostaglandins, and its effect on the opioid system causes pain.33 Chamomile produces analgesia with cholinergic mechanisms in the formalin test.³⁴ Tanacetum parthenium plant has been anesthetized in the plate by affecting the inflammatory processes.³⁵ test Eggplant has an analgesic and cholinergic pathway.³⁶ The bang grain plant has an analgesic effect with cholinergic and opioid mechanisms.³⁷ The fiveseeded plant has an analgesic effect by inhibiting the synthesis of prostaglandins and other inflammatory mediators.³⁸ Artemisia has an analgesic effect by stimulating GABA receptors.³⁹ The herb tea also has analgesia by inhibiting the COX-1 and 5-LO enzymes.40 Iranian lettuce causes central nervous and environmental mechanisms.⁴¹ In sum, it can be said that medicinal plants have substances that can have a medicinal effect to treat a variety of diseases⁴².

The anti-nociceptive effects of these herbs and their potentials through inflammatory processes, inhibition of the release of arachidonic acid, synthesis of prostaglandins and its effect on the opioid system, with peripheral anti-nociceptive mechanism and cholinergic pathways, stimulation of GABA A receptors, COX-1 and 5-LO and central and environmental mechanisms.

| Scientific name | Herbal name | Local Name | Effects |
|---------------------------|-------------------------|---------------|---|
| Lavandula officinalis | Lamiaceae | Ostokhodous | Lavender extract at a dose of 400 mg/kg body weight significantly increased the delay in responding to the stimulant at 5 and 10 minutes after the start of the test and had an analgesic effect. ⁹ |
| Scrophularia striata | <u>Scrophulariaceae</u> | Teshnedari | Administration of Scrophularia striata extract at doses of 100 and 200 in the acute phase reduced the pain sign compared to the control arm. 10 |
| Vitis vinifera | <u>Vitaceae</u> | Angour | The results of a study showed that grape seed extract, on the first phase of pain, was more than aspirin and less than morphine. The analgesic effect of it was not significantly different in the second phase of pain, less than morphine and aspirin. ¹¹ |
| Matricaria recutita | <u>Asteraceae</u> | Babouneh | Chamomile extract with a dose of 25 mg/kg has an acute analgesic effect. ¹² |
| Solanum melongena L. | <u>Solanaceae</u> | Bademjan | Eggplant with a dose of 1000 mg/kg reduced the acute and chronic pain of formalin test. ¹³ |
| Hyoscyamus niger | <u>Solanaceae</u> | Bangdaneh | The bang grain extract with doses of 500, 1000 and 2000 mg. The statistical analysis of the data shows that injection of hydroalcoholic extract of bang-a-grain seed in the doses tested showed significant acute and chronic pain due to formalin test in comparison with The control group decreases ¹³ . |
| Achillea millefolium | <u>Compositae</u> | Boumadaran | Yarrow extract with doses of 25, 50, 75 and 100 mg / kg of mice increased morphine analgesic effect $^{\rm 13}.$ |
| Propolis | propolis | Propolis | Propolis with a dose of 200 mg/kg reduced symptoms of acute pain in the acute phase ¹⁴ . |
| Vitex agnus castus | Lamiaceae | Panjangosht | A dose of 565 mg / kg of hydroalcoholic extract of five-fingered plant significantly reduced chronic pain ¹⁵ . |
| Malva Parviflora | Malvaceae | Panirak | Pump extract of 600 mg dose has a significant relief effect on both acute and chronic pain induced by formalin method. In the acute phase of acute pain with opioid receptor blockage, its analgesic effect was eliminated by naloxone, but this effect was weaker in the phase of inflammation than aspirin ¹⁶ . |
| Cinnamomum Zeylanicum | Lauraceae | darchin | The extract of cinnamon at a dose of 500 mg/kg reduced the second stage of pain (chronic pain) significantly in formalin test compared to the control group ¹⁷ . |
| Artemisia herba alba | <u>Asteraceae</u> | Dermaneh | Artemisia extract with doses of 300, 500 and 1000 mg in the first and second stages of formalin test and control group test. The antinociceptive effect of the extract was dose dependent ¹⁸ . |
| Elaeagnus angustifolia.L | <u>Elaeagnaceae</u> | Senjed | The leaf extract of doses 25, 50 and 100 mg, depending on the dose, had a satisfying effect on the pain caused by formalin injection, and this effect was stronger than the diclofenac drug ¹⁹ . |
| Anethum graveolens | Apiaceae | Shevid | Hydroalcoholic extract of the dose of 500 mg / kg showed a significant difference with the saline group during the duration of analgesia ²⁰ . |
| Phoenix dactylifera | Arecaceae | Tarouneh | Various doses of Garanthus extract of 2, 20 and 200 mg / kg have been reduced in an antimicrobial-induced pain due to Armone formalin in mice ²¹ . |
| Hypericum perforatum L | <u>Hypericaceae</u> | Alafe chay | The antinociceptive effects of intraperitoneal injection of aqueous extract were compared to 200, 400 and 800 mg/kg of Hypericum extract with sodium salicylate as a positive control. The aqueous extract in all doses of analgesia increased in both phases of formalin test, but sodium salicylate was effective only on the second phase of formalin test ²² . |
| Ziziphora cliniopodiodes | Lamiaceae | Kakouti | The antinociceptive effects of 75 mg coccidiary plants in mice compared with indomethacin ²³ . |
| Lactuca sativa longifolia | <u>Compositae</u> | Kahouye irani | In one study, an effective analgesic effect of Iranian cucumber plant with a dose of 660 mg is demonstrated and used in traditional medicine. In addition, it seems that one of the possible mechanisms of action of the extract is opioid pathways ²⁴ . |
| Tanacetum parthenium | <u>Asteraceae</u> | Mokhalaseh | The results of one study showed that the extracts of ethanol extract in different doses of the extract, doses of 30 and 40 mg / kg had more analgesic effects ²⁵ . |

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Table 2: Herbal plants



Lavandula officinalis



Hyoscyamus niger



Scrophularia striata



Achillea millefolium



Cinnamomum Zeylanicum



Artemisia herba alba



Elaeagnus angustifolia.L



Anethum graveolens



Phoenix dactylifera



Vitis vinifera



Matricaria recutita



Solanum melongena L.



Propolis

Vitex agnus castus



Malva Parviflora

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Hypericum perforatum L



Ziziphora cliniopodiodes



Lactuca sativa longifolia



Tanacetum parthenium

CONCLUSION

A variety of indigenous herbs in Iran have been used by traditional healers for the management of pain and/or sedation. Although some scientific studies have been done, but the subject remains largely unexplored. Multinational studies with high-tech, and big investment might lead to discovery of safer and more effective analgesic drugs.

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Authors' contribution: All of the authors took part in writing, reviewing and editing the manuscript.

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Honors & Awards

Professor Fazal H. Khan and Professor Naveed Masood have been awarded the covet Life Time Achievement Award by Pakistan Society of Anesthesiologists, Karachi chapter, in 39th Annual conference of the chapter. Editorial Board congratulates both eminent scholars on recognition of their meritorious services in promotion and progress of the anesthesiology.



Prof. Naveed Masood, Prof. Fazal H. Khan