



A Review Study on the Effect of Iranian Herbal Medicines on Opioid Withdrawal Syndrome

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Abstract

Addiction is a chronic and recurring disease that recurrence phenomenon is the most important challenge in treatment of this disease. Recent experiences have shown that synthetic drugs have undesirable side effects. Recent studies on medicinal plants have shown that they might be effective in treatment of different stages of addiction with lower side effects and costs. The aim of this study was to review the effects of medicinal plants in the treatment of morphine addiction in experimental animals. In this review article, by using keywords of morphine, withdrawal, and plants or herbal medicine in databases of indexing cites, desired articles were obtained since 1994. Inclusion criteria for selecting articles were the articles related to application of medicinal plants in decreasing symptoms resulting from morphine withdrawal were selected. Results of this study on experimental studies have shown that medicinal plants such as *Trachyspermum copticum* L and *Melissa officinalis* decrease the symptoms of withdrawal syndrome in a dose-dependent. Also, medicinal plants like *Avena sativa*, *Hypericum perforatum*, *Passiflora incarnata*, *Valeriana officinalis*, *Satureja hortensis* L, and *Mentha piperita* can have effects on behavior, emotions, and other problems of addicts, decreasing withdrawal symptoms. Results of this study showed that medicinal plants can be effective in controlling deprivation, decreasing dependency creation, and possibly **detoxification** of opioid addicts.

Keywords

addiction, medicinal plants, opioid, morphine

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Addiction to opioids, including morphine, is one of the biggest concerns of health system that imposes high economical costs to society by afflicting many humans.¹ Addiction is a recurring chronic disease² and the recurrence phenomenon is the most important challenge in its treatment.³ It is estimated that 230 million people use illegal drugs at least once a year and 27 million people are addicted, and more important, 12 million people suffer a moderate to severe disability attributable to illegal drug use, and of these, more than 200 000 people die each year from drug use, without the numbers on death and disability linked to alcohol use.⁴

Addiction treatment is a planned action, aimed at achieving abstinence or reducing substance abuse, reducing or preventing the severity and frequency of relapse, and improving the adaptive functioning in abused subjects.⁵

Various kinds of addiction treatments have been developed, including the use of a variety of pharmacological, psychological, and social approaches. The duration of treatment lasts from a few days to years depending on the subjects' needs and the availability of resources.²

Dropout or failure to complete treatment, is also common. Dropout rates range from 24% to 50% in outpatient treatment,⁶

17% to 57% in inpatient treatment,⁷ 32% to 67.7% in substitution treatment,⁸ and from 18% to 44% in detoxification centers.⁹

Consumption of morphine and its combination with other products is increasing in developing countries. Therefore, proper treatment is needed.¹⁰ Continuous consumption of narcotic drugs, including morphine, creates short-term and constant changes in neuron performances sensitive to opioids by stimulating adaptive mechanisms and affects the synaptic plasticity mechanism of nervous structure. Constant changes

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created in brain, interaction between opioid drugs and synaptic plasticity in different areas of brain creates recurrence phenomenon and causes addicts to remain vulnerable to relapse after years of abstinence.¹¹

The problem of addicts after stopping the use of morphine is withdrawal syndrome. The main symptoms of the syndrome include physical symptoms like nausea, perspiration, mydriasis, tachycardia, bellyache, articular and muscular pains, reduced appetite, and mental symptoms like pain, insomnia, anxiety, stress, depression, stimulation can be stated.¹² Various drugs are used to prevent or treat addiction.^{13,14} However, experiences in recent decades have shown that pharmaceutical drugs used to stop morphine use have undesirable and harmful side effects and available remedies have limited effectiveness.¹⁰ On the other hand, medicinal plants have natural effective substances that can affect body biochemical activities by imposing less side effects and costs than pharmaceutical drugs.¹⁵ These medicinal plants have been shown to have promising effects on various diseases,¹⁶⁻²¹ in addition to having the ability to reduce pain²¹ and addiction.^{22,23} The aim of this study was to review effect of medicinal plants in morphine addiction treatment in experimental rats.

Method

In this review article, by studying keywords of morphine, withdrawal, and plants or herbal medicine, in databases of Google Scholar, SID, PubMed, and some other indexing cites, or traditional books, desired articles were obtained since 1994. Inclusion criteria for selecting articles were determined as all original articles related to the research topic. Then, the articles related to application of medicinal plants in decreasing symptoms resulting from morphine withdrawal were selected.

Results

Trachyspermum copticum L

Trachyspermum copticum L is an annual and herbaceous plant that grows in eastern areas of Iran, India, and Egypt. This plant has antispasmodic effects.²⁴ According to research conducted in 2004 to study aqueous extract of this plant fruit in the treatment of morphine addiction in male rats, *Trachyspermum copticum* L aqueous extract at dosages of 10% was effective in jumping, diarrhea, and preventing weight loss in withdrawal syndrome symptoms.²⁵ Other study performed to determine the effects of *Trachyspermum copticum* L extract injected in nucleus of paragigantocellularis on symptoms due to morphine withdrawal syndrome in addict male rats, a dosage-dependent decrease was shown in more qualitative symptoms of withdrawal syndrome.²⁶

Melissa officinalis

Melissa officinalis, which grows in different regions of Iran,²⁴ has analgesic, antianxiety, sedative, antispasmodic, and hypnotic properties.²⁷ According to a study performed in order to

investigate the effects of aqueous extract of *Melissa officinalis* branches on symptoms resulting from morphine withdrawal in male rats, the extract of *Melissa officinalis* with dosages of 10 and 25 mg/kg, dose dependently had significant reduction on the number of jumps and defecate weight, 30 minutes before naloxone injection, in comparison with control group.²⁸

Melissa officinalis, through reduction of the activity of serotonin and binding to γ -aminobutyric acid A (GABA A) receptor, reduces anxiety and in this way offsets the signs of morphine withdrawal syndrome. It has been shown in a study that intracerebral and intraperitoneal injection of GABA A, agonist receptor decreased the naloxone-induced jumping in morphine withdrawal syndrome in mice.²⁹ It is likely that some of the observed effects of *Melissa officinalis* extract are induced by binding to the GABA A receptor.

Ferula persica L

Ferula persica L is another plant that grows in Shahmirzad region in Semnan (Iran) and that has many food applications and has been used extensively in traditional medicine.¹¹ It has different effects on nervous system, including analgesic, anticramp, and antispasmodic activities on ileum contraction.²⁹ Hydroalcoholic extract of aerial parts of *Ferula persica* L in dosages of 50, 100, and 200 mg per kilogram of body weight did not decrease the number of jumps resulted from naloxone injection in addicted rats compared with the control group. However, antispasmodic action of the plant on ileum causes decrease in defecation in animals.³⁰

Avena sativa

Avena sativa is a sedative and neurotonic and is used in traditional medicine to treat anxiety and insomnia, especially in addicted subjects.¹⁵ The combination of the alcoholic extract of *Avena sativa*, *Hypericum perforatum*, *Passiflora incarnata*, and *Lavandula officinalis* (post and cotreated) have been shown to significantly reduce morphine withdrawal symptoms. Administration of the extract cocktail prior to naloxone induced precipitation of withdrawal syndromes also reduced the expression of syndrome signs.³¹

Lavandula officinalis

Lavandula officinalis has antispasmodic, antidepressant, and sedative effects and reduces withdrawal symptoms.^{24,32}

Hypericum perforatum

Hypericum perforatum, other than being an anti-addictive, is a sedative and neurotonic plant. *Hypericum perforatum* is used by many people, especially in Europe, as traditional drug.³³ This plant is used to treat neurological diseases, especially depression.³⁴ In a study performed in 2009, inhibitive effect of this plant on morphine withdrawal syndrome was investigated. According to these results, behaviors of morphine withdrawal syndrome, including jumping, standing, and bruxism in

rats were significantly decreased when *Hypericum perforatum* extract was used along with morphine consumption.³⁵ Spasmodic, analgesic, and antimigraine effects.

Hayprsyn in the plant inhibits the enzyme activity of monoamino oxidase and is used to treat depression. The most authoritative scientific works such as basic and clinical books, including Martindale and PDR (Physician's Drug Reference), approved³⁶ the antidepressant effect of this plant. Hyperisin in this plant inhibits the activity of monoamino oxidase, inducing antidepressant activity.

Passiflora incarnate

Passiflora incarnate is a plant with antispasmodic and antianxiety effects.^{24,37} In a study by Kerachian et al,²³ the effects of 4 plants—*Hypericum perforatum*, *passiflora incarnate*, *Lavandula officinalis*, and *Avena sativa* (each 25%)—in decreasing morphine withdrawal symptoms showed very good effect. During this study in both groups, either extract injection during daily morphine injection for inhibitive effect of extract on physical dependence creation, or posttreatment (extract injected after dependence creation), withdrawal symptoms, including behavior of standing on 2 feet, body stretching, jumping, toe vibration, blink and ptosis were tested over a 30-minute period. Findings of this test showed significant decrease in more symptoms between control group and both groups of during and posttreatment. This decrease was more evident in the group that was given the extract along with morphine.¹⁵

Flavonoid krazzyn obtained from *Passiflora incarnate* showed antioxidant and antianxiety activities. In vitro studies have shown that krazzyn binds a type of GABA A receptor that is called benzodiazepine receptor. Another study showed that krazzyn is able to control withdrawal symptoms of morphine.³⁸

Valeriana officinalis, *Satureja hortensis* L, and *Mentha piperita*

Valeriana officinalis or Valerian has sedative, antispasmodic, antianxiety, antipain, and hypnotic effects in human and experimental animals.³⁹ *Satureja hortensis* L is an herb of that Labiatae family that shows antipain and antispasmodic properties.⁴⁰ *Mentha piperita* is an aromatic plant that has antipain, antispasmodic, and neurotonic properties.^{41,42} In the study by Vafaei et al,⁴³ effects of aqueous extract of *Valeriana officinalis* root, aerial parts of *Satureja hortensis* L, and hydroalcoholic extract of aerial parts of *Mentha piperita* on symptoms due to morphine withdrawal in male rat were investigated. According to the results of this study, 25 mg of *Valeriana officinalis* extract, 200 mg of *Satureja hortensis* L, and 50, 100, 200 and 500 mg/kg of *Mentha piperita* decreased significantly the number of jumping episodes due to naloxone injection to addicted animals. Also, 5 and 100 mg of *Valeriana officinalis*, 25, 50, 100, and 200 mg of *Satureja hortensis* L, and 50, 100, 200, and 500 mg/kg of *Mentha piperita* significantly decreased defecation.⁴² *Portulaca oleracea* L is a herbaceous and meaty plant that has antispasmodic and muscle relaxant properties.⁴⁰

Portulaca Seed

Portulaca seeds at dosages of 25, 50, and 75 mg decreased number of jumps significantly 30 minutes before naloxone injection to addicted animal and caused significant decrease in defecation.⁴³

The results of a study indicated that *Portulaca* extract could decrease morphine dependence in mice. Both extracts of *Portulaca* reduced the jumping episodes dose-dependently. The maximum effect was observed at doses of 0.28 and 1.4 g/kg for the aqueous and ethanolic extracts, respectively. The extracts and clonidine also decreased the total activity in locomotion test.³¹

Benincasa hispida

Fresh extract of *Benincasa hispida* has useful effects in neurological diseases, including spasm and nociception in experimental animals.⁴⁴ According to a study performed in 2000, edible injection of *Benincasa hispida* fresh extract caused significant decrease in number of jumps and amount of defecation in morphine-dependent rats.⁴⁵

Areca catechu

In one study, intraperitoneal injection of 125 and 175 mg/kg of *Areca catechu* dichloromethane extract dose-dependently delayed beginning of jumping, and decreased amount of urination and defecation in naloxone-induced withdrawal in morphine-addicted rats.⁴⁶

Papaver rhoeas L

Papaver rhoeas L is used as an analgesic, anti-inflammation, sedative, and narcotic and also in the treatment of an extensive range of diseases like diarrhea and sleeping disorders.²⁴ In a study in rat, the hydroalcoholic extract effect of *Papaver rhoeas* L on morphine dependence and development was studied. Injection of this extract, 30 minutes before naloxone injection and in dosages of 25, 50, and 100 mg/kg decreased number of jumping and diarrhea dose-dependently. This is while extract injection 30 minutes before morphine injection and in mentioned dosages, increased the number of jumping and diarrhea.⁴⁷

Rosmarinus officianalis

Rosmarinus officianalis is a plant that has many traditional uses worldwide.⁴⁸ In one study, intraperitoneal injection of 2.4 and 1.68 g/kg of *Rosmarinus officianalis* aqueous extract and 0.96 g/kg of alcoholic extract caused decrease in number of jumps in morphine-dependent rats.⁴⁹

Crocus sativus

Pappus of *Crocus sativus* having golden color and pleasant flavor is a widely used plant that has antidepressant and antianxiety properties.⁵⁰ Alcohol and aqueous extracts of saffron

dose-dependently decreased the number of jumps in morphine-addicted rats.⁵¹

Saffron extract contains several constituents, including safranal, crocin, and crocetin, which may affect several physical and psychological signs of morphine dependence. Administration of saffron extract was shown to reduce morphine sensitization and morphine tolerance. Also aqueous and ethanolic extracts could have interaction with the opioid system to reduce withdrawal syndrome in morphine dependent animals.⁵²

Withania somnifera

Withania somnifera is commonly used in Eastern countries, Africa, and India to treat diseases, including neurological diseases.⁵³ According to a study in 2009 the use of this plant with morphine in male rats decreased symptoms resulting from morphine withdraw.⁵⁴

Delphinium denudatum

Delphinium denudatum plant has antispasmodic property in rats⁵⁵ and has extensive range of antistress activities on different stressors.⁵⁶ In one study, effect of methanolic extract of *Delphinium denudatum* on inhibiting morphine withdrawal symptoms in 3 groups of rats that were pretreated, posttreated, or simultaneously treated with morphine was investigated. According to results of this study, *Delphinium denudatum* extract in all 3 groups of animals decreased the symptoms resulting from morphine withdrawal. The maximum effect of the extract in decreasing symptoms was observed in posttreatment group with 700 mg/kg dosage, in simultaneously treated with 700 mg/kg dosage, and in pretreatment with 350 mg/kg.⁵⁷ The dosages of *Delphinium denudatum* given in this study (especially 700 mg/kg) are large. How would these doses be adjusted and administered in humans and the safety of plant in these doses is not clear and should be established.

Peganum harmala

Harmelin available in *Peganum harmala* is a monoamine oxidase inhibitor and can eliminate and sedate withdrawal symptoms. Maximum effectiveness has been attributed to berberine, which is one of the alkaloids available in Berberies plant.⁵⁸ *Berberis vulgaris* L in low dosages has antianxiety properties.⁵⁹

Discussion

With regard to the fact that thymol is the substance most widely available in *Trachyspermum ammi* plant, possibly its therapeutic property is related to this substance. This plant—by affecting serotonergic, cholinergic, GABA A, and 2a adrenergic systems—can have an effect on decreasing symptoms due to morphine withdrawal.²⁵ Also, nucleus paragigantocellularis is one of the most important areas related to addiction. Injection of *Trachyspermum ammi* extract in this nucleolus, through decreasing the amounts of aspartate and glutamate, decreases qualitative symptoms of withdrawal syndrome.²⁶ The ability

to express anxiety effects in stressful conditions in morphine-dependent rats may accrue more rapid without imposing any effect on their motor activity.

Anxiety is considered as one of the strong factors in tendency to receive drug.⁶⁰ Anxiety can play a crucial role in preferential increasing of morphine dependence in rats in the conditioned place preference test and interest in morphine can be decreased in dependent animals when anxiety is treated. So, with regard to antianxiety and sedative effects of *Melissa officinalis* extract, possibly effects of preferential increase in the conditioned place preference test is decreased and so can regulate morphine withdrawal symptoms. Citronella available in this plant reinforces sleeping and decreases muscle tone.⁶¹ Of other effective factors in decreasing symptoms due to morphine withdrawal syndrome in *Melissa officinalis*, the acetylcholinesterase activity and binding to GABA A receptor can be quoted.²⁸

Terpenoids and menoperin available in the *Ferula persica* L plant possibly causes sedative and hypnotic activity of this plant. This plant contains antispasmodic compounds on smooth muscles and lacks compounds that affect decreasing number of jumps. So, possibly the hydroalcoholic extract of *Ferula persica* L has not effect on symptoms resulted from morphine withdraw, and only has hypnotic effects and is effective in decreasing diarrhea dose-dependently.³⁰ Benzoflavone available in *Passiflora caerulea* causes synaptic inhabitation by affecting one of the GABA receptors and is effective in decreasing pain and anxiety by providing significant decrease in activity of central nervous system. Furthermore, this compound prevents weight decrease. Linalool available in *Lavandula* also has sedative and analgesic effects.⁶² *Hypericum perforatum* inhibits P450 cytochrome isoenzymes, and so this plant can be used to increase half-life of common drugs used in morphine withdrawal. Of other mechanisms effective in inhibition of symptoms by *Hypericum perforatum* is the inhibition calcium binding to voltage-dependent calcium channels in presynaptic membrane that causes induction of antispasmodic effects of this plant. Different studies have shown that seeds of *Avena sativa* without harmful effects can significantly sedate the nervous system. As mentioned before, one of the main and problematic symptoms of withdrawal syndrome is anxiety that *Avena sativa*, *Hypericum perforatum*, and *Passiflora caerulea* plants are effective in decreasing by complementing each other's effects.²⁹ Valerian and valeinic acid of *Valeriana officinalis* derivatives imitate GABA A activity and increase release of GABA intermediate and decrease its reuptake. So, antispasmodic, analgesic, antianxiety, and hypnotic effects of *Valeriana officinalis* are justifiable. Also the mentioned plant creates antispasmodic effect by influencing calcium channels or affecting on digestive system directly. Carvacrol and flavonoid in *Satureja* causes analgesic effects. *Mentha piperita* decreases pain by affecting kappa-opioid receptors and inhibiting pain signal transfer.

Portulaca is rich in potassium ion and contains flavonoids, mosulgae, and pectin. These compounds act as muscle relaxants and decrease diarrhea. Also, this plant, by having antianxiety

effect⁶³ and affecting internal opioid receptors, causes the preferential increase in the conditioned place preference test; hence, it decreases and regulates symptoms of morphine withdrawal syndrome.²⁶ Compounds in honeydew that affect withdrawal syndrome are possibly triterpene, sterol, and glycoside.⁴⁵ As was mentioned in Results section, *Delphinium denudatum* plant has extensive antistress activity and limits morphine physical dependence but its performance mechanism is not yet determined.⁵⁷ Possibly *Papaver rhoeas* L causes limitation in symptoms resulting due to morphine withdrawal by anticholinergic and antidopaminergic activity.⁴⁷ Rosemary contains alkaloids, saponins, tannins, and flavonoids that impart analgesic properties. Possibly, this plant decreases morphine withdrawal symptoms through GABA system.⁴⁹ *Hypericum perforatum* decreases temptation by benefiting opioid antagonists and decreases symptoms resulting from morphine withdrawal in addition to its anti-depression properties.⁶⁴

Saffron contains sedative and antianxiety compounds that cause increase in sleep duration and decrease in withdrawal symptoms by its hexobarbital. Possibly compounds like flavonoids and crocin pigment are effective in decreasing these symptoms.⁵¹ Also dichloromethane available in *Areca catechu* extract inhibits monoamine oxidase enzyme and increases bioavailability and neurological transfer of serotonergic and noradrenergic system.⁴⁶ Which system is involved in reduction of withdrawal symptoms is not clear. Pretreatment with *Withania somnifera* extract also causes protection of structural changes (decreasing density of dendritic thorns of nucleus accumbens).⁴² Ginseng decreases anxiety and depression in withdrawal syndrome through corticotrophin-releasing factor system, and hypothalamic neuropeptide Y.⁶⁵

It should be noted that withdrawal syndrome is accompanied with sever increase in oxidative stress.⁶⁶ Most of medicinal plants possess antioxidant activity,⁶⁷⁻⁷⁰ thanks to polyphenolic compounds such as flavonoids, flavonols, and anthocyanins.⁷⁰⁻⁷³ Oxidative stress is involved in several difficult-to-cure diseases such as diabetes,⁷⁴⁻⁷⁶ atherosclerosis,^{77,78} cardiovascular diseases,^{79,80} cancer,^{81,82} Alzheimer's disease,⁸³ gastrointestinal disorders,^{84,85} and infectious^{86,87} diseases. Medicinal plants with antioxidant activities have been able to counteract the development of these complications.⁸⁸⁻¹⁰² Therefore, the plants effective in withdrawal syndrome should counteract, at least in part, oxidative stress induced through withdrawal syndrome, thereby reducing its symptoms. The antioxidants usually scavenge the free radicals that cause oxidative stress.¹⁰²⁻¹¹¹

Conclusion

Results of this study showed that medicinal plants can be effective in decreasing dependence, controlling withdrawal, and possibly detoxication in rats. The use of combined extracts of several plants that have antianxiety, antispasmodic, analgesic, and antidepressant effects with suitable dosage in morphine withdrawal should be examined in experimental models.

Author Contributions

All the authors wrote the first draft of the manuscript equally. MRK revised and edited the last version.

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Ethical Approval

In preparation of this review paper we tried to consider all Ethical issues.

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