

The Therapeutic Effects of Medicinal Plants on Depression and Anxiety Disorders

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Abstract

Anxiety and depression are among the commonly occurring illnesses around the world that cause changes in the lifestyle of humans and impose huge costs to treat these disorders on human societies. These disorders can be associated with physiological symptoms such as tachycardia, sweating, respiratory dysfunction, numbness, and sometimes paralysis of the limbs, etc. In the treatment of these diseases, the goal is to help people to minimize the risk of following side effects while healing these disorders. In the treatment of drugs in the past, benzodiazepine drugs such as diazepam (valium), alprazolam (xanax), lorazepam (ativan), and baspiron were used to treat anxiety disorders. However, presently anti-depressant drugs such as fluxetin, paroxetine, sertaline, and venlafaxine are more widely administered. It is estimated that between 10 to 20% of people in the western hemisphere use these drugs almost regularly. In depression studies, monoamine neurotransmitters such as serotonin (5- HT), neuroadrenaline (NA) and dopamine (DA) play an important role in mediating depressive behaviors. Various studies have shown that major depressive symptoms are caused by a reduction in the function of these neurotransmitters. Monoamine oxidase enzyme (MAOA) is also a key enzyme dependent on the metabolism of neurotransmitters, and it has been suggested that its activity is one of the indicators of psychosomatic susceptibility. It has also been observed that the hypothalamic-pituitary-adrenal axis (HPA) is impaired in patients with depression. The use of herbal medicine has been commonplace in ancient civilizations, and hence since ancient times plants have long been an important source of medicine. Research on plants in recent years has shown that plants such as chamomile and lavender, which have formerly been used to treat anxiety and depression have anti-anxiety and anti-depression effects; accordingly, in the present study, the effects of 18 plant types on the treatment of these disorders have been investigated.

Key words: Medicinal Plants, Depression, Anxiety

Introduction

Anxiety is one of the common psychiatric disorders that is accompanied by unpleasant and vague feelings, restlessness and insomnia and different drugs are used to treat anxiety (1-3). Depression and anxiety disorders are the most common psychiatric disorders that are defined as negative emotional experiences and associated with biochemical, cognitive, behavioral, and psychological changes (4, 5). Anxiety and depression are very common disorders that afflict many people and are associated with physiological symptoms such as tachycardia, sweating, respiratory

dysfunction, numbness and sometimes paralysis of the limbs, insomnia, aggression, etc. (6, 7). Studies show that among behavioral problems, anxiety and depression are the most frequent ones (5). These disorders are differently observed in both sexes (8, 9), and the rate of depression and anxiety disorders in men is about half that of women (10). Frequent and prolonged anxiety is usually associated with physiological responses, including increased metabolism, decreased immunity and increased cardiovascular function. There is also an important relationship between anxiety and subsequent

deaths, indicating the importance of this disorder as a public health and wellness issue. Several studies point to the role of serotonergic and GABAergic systems, as well as oxidative disorders in the development of anxiety and depression (11, 12). Depression is one of the common psychiatric diseases for which there are various therapies. Studies have shown that the use of antioxidant compounds abundantly found in plant enzymes is effective in treating people with depression and anxiety disorders (13, 14). Anxiety and stress, which are among the most important and common disorders in human societies, are the causes of many other illnesses (15). The results of studies in recent years emphasize the role of oxidative stress in the development of anxiety disorders (16). Researchers have done a lot of research into the mechanisms involved in the development of anxiety and depression disorders, and so far they have proposed several methods for the treatment of these disorders using synthetic and herbal drugs (17). Medicinal plants have long been used as a therapeutic approach (18). Due to the tendency of different humans around the world to the use of medicinal herbs and the relaxing features of some plants, as well as the reduction of the complications of chemical drugs, the consumption of herbs is increasing (19). Since the use of synthetic drugs to treat depression and anxiety disorders generally has side effects, in recent years, the use of herbal medicines in the treatment of these diseases has attracted the attention of researchers and medical specialists. In this vein, the present study examines the effects of the extracts of 18 plant species studied from 2000 to 2018.

Wild Poppy

Papaveraceae plants including wild poppy, known scientifically as *Papaver rhoeas*, have a variety of alkaloids, and to date various drug properties of theirs have been reported. Extract of wild poppy having different alkaloids such as radin, radic acid, papaveric acid, macoic acid and mucilase, has similar effects to poppy

and due to the presence of very small amounts of morphine in the extract of this plant, it is called "tongueless opiate"(20). Osanloo *et al.* (2016) reported that consumption of 10, 30 and 100 mg / kg of hydroalcoholic extracts of wild poppy resulted in improved depression in rats. The researchers stated that improving depression in rats receiving the hydroalcoholic extracts of wild poppy was dose dependent (21). Also, the results of one study showed that the alcoholic extract of wild poppy reduced the levels of anxiety and corticosterone, and as a result stress levels that cause many other illnesses (15). Since the disruption of the hypothalamic- pituitary-adrenal axis and the regulation of corticosterone levels in the blood is one of the causes of anxiety disorders (22), our study showed that the extract of wild poppy helps to reduce corticosterone levels in the blood, hence wild poppy extract reduces the level of anxiety in rats due to decreased levels of above-mentioned hormone (15).

Borage

Persian borage plant with the scientific name *Ecgium amoenum (L.)* belongs to Boraginaceae family that grows wild in most European countries (23) and also in parts of northern Iran (3). The effective ingredients in this plant include, but are not limited to, anthocyanidine, flavonoid aglycone, and gamma-fatty acids, and because of these compounds, the anticonvulsant effects of this plant have been demonstrated in animal studies (24). It has been shown that a 14-day consumption of borage in humans reduces the peroxidation of blood lipids, which may be due to bioactive compounds such as flavonoids in the extract of this plant (25). Some of these bioactive compounds, such as rosmarinic acid and cyanidin-3-glucoside are anti-inflammatory and inhibiting of the expression of cyclooxygenase 2 (COX-2) gene, respectively (26), resulting in a decrease in the amount of intracellular reactive oxygen species through the activity of glutathione

antioxidant system. Persian borage is a plant with anti-inflammatory (23), anti-depressant, analgesic, anti-bacterial, antioxidant and immunosuppressant properties (28- 32). Today, it is well-known that the chemical compounds present in the borage extract have medicinal value and are effective in regulating animal behaviors and treating anxiety (33). One of our studies also showed that buspirone and borage extract both reduce anxiety levels, and the effect of borage amplified with increasing treatment period (34). Studies have shown that intraperitoneal injection of borage extract has anti-anxiety properties and is useful for the treatment of anxiety disorders (37-35). In a double-blind clinical study, it was shown that the use of aqueous borage extract for four weeks resulted in an improvement in depression in patients with depression (38).

Chamomile

Chamomile with the scientific name *Matricaria chamomilla* is one of the medicinal plants found in wide areas around the world, including Africa, Asia, North and South Americas, Europe and Australia (39). Chamomile is traditionally used in different parts of Iran due to the febrifuge effects, strengthening neurological and immune systems, hypnosis, sedation and analgesia (40). Anti-colic, antiseptic and anti-anxiety effects have also been reported (41). Chamomile extract can improve and enhance avoidance memory in treated rats by improving neuronal structure and preventing neuropathic processes (42). Although the anti-anxiety effects of chamomile plant have not been determined accurately, chamomile seems to exert its anti-anxiety effects, probably due to flavonoids, antioxidants and phytoestrogens, and these effects can be attributed to the binding of agonistic compounds in this plant to benzodiazepine receptors of neurotransmitter gamma-aminobutyric acid (GABA). Various evidence suggests that chamomile flavonoids are likely to be influencing GABA, noradrenaline (NA),

dopamine (DA), and serotonin, or by modulating the hypothalamic-pituitary-adrenal axis have anti-anxiety activity (41).

Passion flower

Passion flower with the scientific name *Passiflora caerulea* is a genus of passifloraceae family that is known throughout the world as a sedative and anti-anxiety drug (43). The passion flower extract contains flavonoid compounds of the Harmala group and cyanidric acid, which has the same antioxidant properties as barbiturates and acts as an agonist of GABA receptors, and, by binding to them, exhibits anti-anxiety effects (44). Anxiety is the most prevalent preoperative sensation that can affect postoperative outcomes. Based on the results of a study, the use of oral drops of passion flower before orthopedic surgery helps reduce the patient's anxiety and therefore, the use of passion flower extract for anti-anxiety and sedation therapy is recommended (45). In postmenopausal women, the risk of depression, anxiety and stress increases with respect to women's mental health. More than 50% of postmenopausal women suffer from one or more physical symptoms, such as back pain along with itching, night sweats, skin rash, osteoporosis, and mental anxiety. In a clinical study, it was shown that six weeks of passion flower consumption was associated with an improvement in menopausal symptoms such as headache, insomnia, depression and anger (46).

Valerian plant

Valerian plant or valeriana known scientifically as *Valeriana officinalis* belongs to the family of Valerianaceae. Valerian plant has healing properties in some nerve disorders, insomnia and hysteria (47). It has been shown that valerian plant extract has sedative, hypnotic and anti-depressant effects having effective compounds such as isovaltrate, valproate and didrovaltrate (48). Valerian plant extract has anti-anxiety effects having

valepotriate compounds which can be used to control anxiety after further investigations (6, 7). It has been shown that valerian extract exerts its anti-depressant effects through interference with serotonin, GABAergic and adenosine systems (49). In addition, the results of a study show the antidepressant effect of valerian extract by stimulating neurotransmitter serotonin biosynthesis in the brain (50).

Saffron

Saffron plant, called scientifically *Crocus sativum L.*, belongs to the family of Iridaceae (51), which is found in the northeastern parts of Iran, and flavonoid, anthocyanin and tannin compounds are found in its flower extract (52). The bitter taste of saffron is due to the presence of a substance called picocrocins. This material is converted into an aromatic aldehyde called saffranal by the thermal or enzymatic decomposition of the plant during processing of the plant. Other carotenoids, such as beta carotene, lycopene and zeaxanthin, and vitamins, especially riboflavin and thiamine, are found in saffron. Crocin, crocetin, and saffranal are the main active ingredients of saffron (51). Saffron has been named as a joyful plant in Iranian traditional medicine, and findings from a study have shown that the aqueous extract of saffron is likely to have an anti-depressant effect through affecting the norepinephrine system of the brain, similar to that of imipramine (53). A study has shown that saffron extract has better anti-depressant effects than fluoxetine (54). It has also been reported in various studies that saffron consumption improves depression levels in patients with depression (55) and cardiac patients (56); also improves anxiety in young people with depression and anxiety (57). Another study showed that crocin, as the main carotenoid of saffron, prevents the reduction of brain dopamine, increase of oxidative factors and degradation of dopamine neurons in the brain (58); therefore, it applies

its antidepressant effects probably due to increased dopamine in the brain.

Lavender

Lavender, scientifically called *Lavandula officinalis* is a plant of Lamiaceae family and one of the herbs used in traditional medicine, which is effective in the treatment of diseases related to the central nervous system such as improving sleep and treating anxiety (59). The researchers attribute this effect to the similar effects of lavender extract to benzodiazepines and increase in the amount of GABA neurotransmitter (60). The presence of effective substances such as monoterpene as well as sesquiterpenes including linalol, linalyl acetate and flavonoids, induce a positive effect on the central system (61). In a study, the sedative and anti-anxiety effects of lavender extract have been attributed to binding to benzodiazepine receptors of GABA_A receptors and it is held that this effect is more than the effects of diazepam (62). Studies have revealed the antidepressant effects of lavender extract, and it has been shown that the effect of this plant on the treatment of depression strengthens the effects of imipramine (59). In another study, it was shown that the use of lavender extract with reduction of anxiety during cesarean section decreases the pain of primiparous women (63). In the treatment of anxiety, conventional drugs such as benzodiazepine medications, which are serotonin-specific reuptake inhibitors, are used (64). In this vein, considering that the use of lavender herb extract stimulates the secretion of neurotransmitters, such as serotonin (65), so it can have anti-anxiety effects. Lavender has been shown to have sedative and anti-anxiety properties and has a significant antidepressant effect similar to fluoxetine (66).

Silybum

Silybum known scientifically as *Silybum marianum* belongs to the family of Asteraceae that has various antioxidant, anti-inflammatory and anti-cancer pharmacological effects. The

effects of cardioprotection, liver protection, neuroprotection and protection against cancer have also been reported for the Silybum plant (67). Research has shown that silybum has high levels of polyphenolic antioxidants and supportive effects in neurodegenerative diseases, and with its antioxidant properties it can improve the symptoms of cognitive and behavioral disorders and decrease GFAP protein levels of brain astrocytes in rats with Alzheimer's disease (68). According to some reports, silymarin, the main active ingredient in silybum, increases the concentration of some neurotransmitters in the brain, and the results of a study also showed that the aqueous extract of silybum in the animal model has an antidepressant effect (69). Silybum has been reported to exert its antidepressant effects through the BDNF / TrkB signaling pathway and enhance the production of neural stem cells (70).

Tarragon

Tarragon plant with the scientific name *Artemisia dracunculus L.* belong to the Compositae family, which having compounds such as monoterpene, sesquiterpene, estragole, ocimene and methylchavicol has antioxidant, anti-diabetic, antibacterial and anti-inflammatory properties (71,72). Tarragon contains several bioactive elements such as flavonoids (flavones, flavanones, dihydroflavanols, and chalcones, and phenolic acids (hydroxybenzoic, caffeic, or 5-O-caffeoylquinic acids, among others) as well as a small amount of vitamin and sesquiterpenoids (73). The most important aromatic compounds of this plant are methyl eugenol, carvacrol, and thymol (74). Anticoagulation, anti-fungal, anticonvulsant, analgesic as well as liver and stomach protecting effects of tarragon have been proven (74). The hydro-alcoholic extract of tarragon extract, probably due to its antioxidant compounds, reduces anxiety and depression in rats exposed to chronic restraint stress (75). It has been reported that natural

and synthetic flavonoids have agonistic effects on GABA_A receptors and, like benzodiazepines, affect GABA_A receptors. Methyl eugenol, a compound of tarragon, has an agonistic effect on GABA_A receptors. On the other hand, the presence of benzodiazepines in tarragon and the use of these agents for the treatment of anxiety reinforce the long-lasting hypothesis of the anti-anxiety effects of tarragon. Thymol also reduces the level of anxiety in rats. Likewise, carvacrol oral administration shows anti-anxiety effects in rats that have been proven by the addition of high-level maze tests. Besides, limonene, a component of tarragon compounds, has anti-anxiety effects (74). Carvacrol reduces depression by affecting the dopaminergic (and not noradrenergic or serotonergic) system (74).

Grape seed

Grape with the scientific name *Vitis vinifera* is a genus of Vitaceae family. Given that antidepressants can exert their effects with increased norepinephrine, serotonin, and brain-derived neurotrophic factors (76), therefore, as shown in another study, grape seed extract improves the degrading effects of brain ischemia in rats due to its antioxidant effects and the stimulation of neurotrophic factors secretion (77). Thus, grape seed extract can have anti-depressant effects. Based on the results of a study, grape seed oil can reduce the level of anxiety in male rats by inhibiting oxidative stress in a high cross maze model (78). Therefore, considering that grape seed extract is very rich in antioxidant compounds such as cyanidine prostaglandin (80), it can be used to treat anxiety disorders such as anxiety. According to the findings of a study, the extract of mozzarella Grape kernels have flavonoid compounds that reduce the anxiety level in a cross-legged maze test, which is probably done by stimulating GABA receptors and increasing serotonin secretion (81).

Ginger

Ginger with the scientific name *Zinger officinale* from Zingibracea family is one of the medicinal plants that has been widely used in traditional medicine (82) and has long been used in medicine for many years in addition to dietary supplementation. Since the last decades, it has been used for the treatment of various diseases due to the variety of its active compounds. The treatment spectrum of this plant is in the treatment of diabetes (83), rheumatism, asthma, nausea, vomiting, hypertension, dementia, fever and infection and has sedative and anti-anxiety properties. The pharmacological effects of this plant include anti-oxidant, anti-tumor, anti-apoptotic, anti-inflammatory, anti-hyperglycemia, anti-tussive, and anti-cold properties (84). It has been reported that in diabetic patients, the stimulant activity of ginger extract in the serotonin system, which manifests itself as a direct stimulation of 5-HT₃ receptors, increases insulin secretion and reduces blood glucose levels. For this reason, ginger extract can improve the symptoms of diabetes and its associated depression (85).

Salvia

Salvia plant with the scientific name *Salvia limbata* is a genus of the Lamiaceae family that has more than 900 species and is scattered in different parts of the world. Species such as *Salvia urmiensis*, *Salvia sahendica*, *Salvia hypoleuca* and *Salvia persepolitana* are native to Iran. Many studies have been done on *Salvia limbata* species which is widely used in traditional medicine due to its therapeutic effects. This plant contains various compounds such as different flavonoids, tannins and terpenoids like monoterpenes, diterpenes, sesquiterpenes and tetraterpenoid. The pharmacological effects of terphenoids can be analgesic, anti-inflammatory, antihypertensive, anti-oxidant, anti-microbial, sedative, hypnotic and anti-anxiety properties. The use of aqueous and alcoholic extracts of *Salvia limbata* species flowers reduces the threshold

of pain, number of jumps and also anxiety in morphine withdrawal syndrome in mice (86).

Hypericum

Hypericum with the scientific name *Hypericum perforatum* is a plant whose antioxidant properties have been proven (87, 88). Hypericum with an effective ingredient called hypericin and hyperforin, which has an inhibitory effect on the monoamine oxidase enzyme, and by preventing the degradation of serotonin and increasing this neurotransmitter in the brain diencephalon region, as well as having compounds that are agonists of GABA and sigma opioid receptors, exerts its anti-depressant and anti-anxiety effects (89, 90). Hypericum compound contained in hypericum extract has anti-depressant and anti-anxiety effects, and this is similar to the chemical anti-depressant effect of imipramine medication (91). A study on the effect of herb extract on students' anxiety in student dormitories in Karaj showed that this plant has an effect on decreasing the anxiety level in these students and due to the absence of side effects of this herb extract it is recommended in the treatment of anxiety (92).

Cinnamon

Cinnamon with the scientific name *cinnamomum verum* belongs to the Lauraceae family, which has anti-hypertensive agents (93), anti-oxidant, anti-inflammatory, and neuroprotection properties. It has been reported that nourishments such as cinnamon containing antioxidants can control oxidative stress and reduce blood pressure. In fact, cinnamon has its own effects on lowering blood pressure through Peroxisome proliferator- activator receptors and inhibiting the formation of ultimate glycosylated products. Also, there are various phenolic agents in cinnamon such as catechin, epicatechin, procyanidine B2 and phenol polymers that have inhibitory effects on the formation of ultimate products due to glycosylation (93). Also, cinnamon has

antioxidant properties due to phenolic compounds and other antioxidant compounds such as eugenol, camphene, coumarin, cinnamic acid, cinnamaldehyde, cinnacassiol and gamma-terpinene (94). Lead is one of the environmental pollutants that enters the nervous system and leads to disturbances such as depression and anxiety, and it has been shown that cinnamon extract in the rats receiving lead acetate has anti-anxiety and anti-depressant effects (95). Cinnamon extract has antioxidant properties. This property is due to the presence of phenolic compounds and other antioxidant compounds (96).

Basil

Basil plant scientifically called *Ocimum basilicum* L. belongs to Labiatae family, which has antioxidant, anti-inflammatory, anti-apoptotic, anti-diabetic and analgesic properties. In the extract of this plant, compounds such as monoterpenes, limonene, mircin and flavonoids such as quercetin, camforol, rutin, rosmarinic acid, caffeic acid, steroids and vitamins A, C, E and K (97, 98). It has been shown that rosmarinic acid by stimulating the hippocampus-derived neurotrophic factor decreases depression in rats (99). Similarly, camforol also has anti-depressant effects with inhibitory effects of monoamine oxidase enzymes and increased dopamine levels (100). The results of a study in India on the extract of 3 species of *Ocimum* genus show that they have inhibitory activity of monoamino-oxidase enzyme and therefore have anti-depressant activity (101). Basil hydroalcoholic extract reduces anxiety and depression in mice exposed to chronic restraint stress (102). Based on the findings of a study, the antidepressant effects of mentha spicata essential oil resemble fluoxetine, and probably the compounds in it (especially caron) induce their effects with the serotonergic mechanism (103).

Marshmallow

White marshmallow is a plant scientifically

called *Althaea kurdica* from the Malvaceae family and it has been shown that the administration of the extract of this plant can improve the level of anxiety and serotonin in animals exposed to acoustic stress (75). The use of medicinal plants has been common in reducing anxiety and improving sleep disorders since the oldest, and hence white marshmallow has been used for reducing anxiety in Iran for a long time. In one study, aerobic training and injection of marshmallow extract showed to reimburse anxiety levels due to acoustic stress, while the role of aerobic training was greater than that of the white marshmallow (104).

Rosemary

Rosemary plant with the scientific name *Rosmarinus officinalis* L. is a genus of Labiatae family with numerous pharmacological effects, such as liver protection, antibacterial, anti-ulcer, anti-clot, diuretic, anti-diabetes, antioxidant and anti-inflammatory therapies (39). It is reported that the antidepressant effects of the extract of this plant are probably through a monoaminergic system. It has been shown that Ursolic acid, a major component of rosemary plant, has an anti-depressant effect at 0.1 mg / kg concentration in rats and this effect is enhanced in the presence of dopamine receptor agonists and prevented in the presence of its antagonists (2).

Fennel

The scientific name of the fennel plant is *Foeniculum vulgare* and is from the Apiaceae family. It is a herbaceous, aromatic plant with a height of 1 to 2 meters and grows in many regions of Europe, the Mediterranean and Asia. Fennel is rich in phytoestrogens, including lignans (1). The therapeutic effects of fennel plant have been proven in the treatment of hirsutism, osteoporosis, weight gain in the breasts glands, growth of the testicles, treatment of digestive pains, dysmenorrhea and anxiety treatments. The

plant's distinctive ingredients are Antol Trans, limonene and fenchone. Fennel is known as a herb with anti-anxiety effects. It has been reported that fennel exerts its effects through the influence of the GABAergic system and estrogen receptors (1).

Conclusion

Various synthetic and chemical drugs are available for the treatment of depression. However, most patients with depression are not able to withstand the negative side effects of chemical drugs, and only 50 % of the patients are fully recovered. In recent years, we have seen countless research and studies to find new, affordable drugs without side effects to treat depression. In the meantime, herbs have shown positive pharmacological effects in the treatment of depression in various animal and human models. According to the studies reported in this article and considering the side effects of most synthetic drugs used in the treatment of depression and anxiety, it can be argued that since medicinal herbs have higher antioxidant properties and fewer side effects and exert their therapeutic effects through agonistic effects or stimulating the secretion of neurotransmitters, such as GABA and serotonin, they ought to be used based on the opinion of doctors specializing in the treatment of these disorders to treat depression and anxiety disorders. In the end, it should be noted that in most studies on the antidepressant effects of medicinal herbs, their toxic effects have not been evaluated and the margin of safety between therapeutic and toxic effects has not been determined. Therefore, to confirm the safety of consumption, it is recommended that while studying the therapeutic effects of herbs and their active compounds, their toxicity effects should also be considered.

Ethical issues

Not applicable.

Authors' contributions

All authors equally contributed to the writing and revision of this paper.

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