



Medicinal herbs with anti-depressant effects

Mahbubeh Setorki*^{ID}

Department of Biology, Izeh Branch, Islamic Azad University, Izeh, Iran

ARTICLE INFO

Article Type:
Review**Article History:**

Received: 10 November 2018

Accepted: 24 January 2019

Keywords:Depression
Clinical trials
Medicinal plants
Herbal medicines

ABSTRACT

Depression is a life-threatening *chronic illness* which affects people worldwide. Drugs used to treat this disease have multiple side effects and may cause drug-drug or drug-food interactions. Additionally, only 30% of patients respond adequately to the existing drugs and the remaining do not achieve complete recovery. Thus, finding effective treatments that have adequate efficacy, fewer side effects and lower cost seem to be necessary. The purpose of this study was to review animal and double-blind clinical studies on the anti-depressant effects of medicinal herbs. In this study, validated scientific articles indexed in PubMed, SID, Web of Science and Scopus databases were reviewed. A database search was performed using the following terms: clinical trials, depression, major depressive disorder, essential oil, extract and medicinal plant. Positive effects of a number of herbs and their active compounds such as St John's-wort, saffron, turmeric, ginkgo, chamomile, valerian, Lavender, *Echium amoenum* and *Rhodiola rosea* L. in improvement of symptoms of mild, moderate or major depression have been shown in clinical trials. The above plants show antidepressant effects and have fewer side effects than synthetic drugs. Hence, they have the potential to treat patients with depression.

Implication for health policy/practice/research/medical education:

Medicinal plants have the potential to treat patients with depression.

Please cite this paper as: Setorki M. Medicinal herbs with anti-depressant effects. J Herbmed Pharmacol. 2020;9(4):309-317. doi: 10.34172/jhp.2020.39.

Introduction

Depression is a common, debilitating, and dangerous disease that affects the person's life and behavior and influences many people all over the world. Depression currently affects 20% of the global population and is considered as one of the leading causes of death. According to the World Health Organization, depression is ranked fourth among the health problems and major depressive disorder is predicted to become the second most debilitating factor in the world by 2020 (1,2). According to the research conducted in Iran, about 7 million people suffer from depression and about 15%-25% of the population experience depression at different degrees (from mild to severe) (3). In addition to affecting individual performance in various contexts such as education, occupation, and interpersonal relationships, depression increases the rates of misdemeanor and substance abuse. Moreover, depression increases the risk of suicide. The risk of suicide among patients with depression appears to be more than other mental disorders (4).

Studies have shown that changes in brain monoamine level, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, immune-inflammatory processes, oxidative and nitrate stress, neurodegeneration, and inhibition of neurogenesis are involved in the pathogenesis of depression. Various drugs have been introduced for the treatment of depression, including selective serotonin reuptake inhibitors, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors (5).

Clinical trials show that most patients do not like to take the medication due to their side effects. Studies also show that some available drugs are effective only in half of the patients and others do not achieve complete remission (6). Therefore, finding effective treatments for depression with adequate efficacy, fewer side effects and lower cost is one of the active fields of research today (4). In this regard, medicinal plants which show wide spectrum of therapeutic properties have attracted considerable attention as supplementary drug or even alternative treatment for depression all over the world (7). The aim

*Corresponding author: Mahbubeh Setorki
Email: doctor.setorki@gmail.com

of this study was to review animal and clinical studies performed on anti-depressant effects of medicinal plants.

Methods

In this study, validated scientific articles indexed in PubMed, SID, Web of Science and Scopus databases were reviewed. A database search was performed using the following terms: clinical trials, depression, major depressive disorder, essential oil, extract and medicinal plant.

Results

Until today, numerous studies have shown the antidepressant effects of medicinal plants in animal models with fewer studies on human. Plants that have shown considerable activities in animal studies and are used in clinical trials are presented here.

Hypericum perforatum L. (St John's wort)

Common Saint John's wort with the scientific name of *Hypericum perforatum* L. is an herbaceous perennial plant of the family Hypericaceae, which is native to Western Europe, Asia, and North Africa. This plant is widely spread in Iran and grows on the hillsides of the Alborz Mountains, Chalus, Mazandaran and western parts of Iran (8). The importance of this plant as an herbal remedy to treat depression has increased significantly in recent years and several studies have been carried out on its antidepressant effects in animal models as well as humane studies (4). The double-blind randomized clinical trials on patients with mild to moderate depression indicated that the St John's wort extract was more effective than placebo and had effects similar to fluoxetine, imipramine, and sertraline. In addition, its side effects were significantly lower in comparison with the above mentioned drugs (8-12). The main effective ingredients of the herb are hyperforin and hypericin, and studies have shown that hyperforin is a superior option to hypericin for anti-depressant activity of the plant (13). Experimental studies have demonstrated that the plant extract is a weak inhibitor of monoamine oxidase enzyme but significantly inhibits the reuptake of synaptic serotonin, dopamine, and norepinephrine. The plant extract has a downregulative effect on beta-adrenergic receptors and an upregulative effect on serotonin receptors. It also changes the concentration of neurotransmitters in some parts of the brain. It has been stated that the plant extract adjusts the expression of the genes that control the hypothalamic-pituitary-adrenal axis and reduces the elevated levels of serum adrenocorticotropin and corticosterone (4). In a study conducted on women aged 55 to 65 with depression, it was found that after consuming the hypericin extract, the level of 3-methoxy-4-hydroxyphenylglycol significantly increased. Methoxy-4-hydroxyphenylglycol is a metabolite produced by norepinephrine metabolism and is a marker

for anti-depressant response (14). Several pharmaceutical products prepared from this plant include hypericaps, Hypericum STADA, Hypericum 300, and Hypericum Syxyl S. Hypiran drop and Perforan tablet have been made and presented to the market in Iran (13).

Saffron (*Crocus sativus* L)

Saffron with the scientific name of *Crocus sativus* L., from the family Iridaceae, is one of the most expensive spices in the world. In addition to traditional value as a food additive, it also has a number of therapeutic effects. In general, the saffron, its extracts and tinctures have been used in traditional medicine as antispasmodic, analgesic, anti-inflammatory, sedative, carminative, sweat enhancer, expectorant, stimulant, gastric strengthener, sexual desires stimulant and as an agent to develop early menstruation. The antidepressant effects of the aqueous and hydroalcoholic extracts of saffron have been demonstrated in animal models (15,16). In a randomized double-blind clinical trial, 40 patients with mild to moderate depression were treated with hydroalcoholic extract of saffron at a dose of 30 mg/d or fluoxetine at a dose of 20 mg/d. After 6 weeks of treatment, saffron caused considerable improvement similar to that of fluoxetine. In addition, no significant differences were found between the two groups in terms of side effects. One of the side effects reported for saffron is an increased risk of bleeding; but in this study, saffron didn't cause abnormal bleeding (17). In a clinical trial, the saffron capsule at a dose of 30 mg/kg showed antidepressant effects similar to imipramine (100 mg/kg) in patients with mild to severe depression. The anticholinergic effects such as dry mouth and sedation were seen in the imipramine group, which were significantly higher than those in saffron group (18). In another study on women with premenstrual syndrome, the daily consumption of saffron capsules at a dose of 30 mg/kg significantly reduced the symptoms of the disease as well as the depression. Although the side effects of saffron were higher than the placebo, their difference was not significant (7). Regarding the mechanism of antidepressant activity, it is proposed that two active compounds of saffron, including safranal and crocin, inhibit the reuptake of dopamine, norepinephrine, and serotonin (15).

Rhodiola rosea L.

Rhodiola rosea L., from Crassulaceae family, naturally grows in Europe, Asia, and North America. This herb has long been used in the traditional medicine of these areas to treat various disorders, including anxiety and depression. Currently, *R. rosea* is known as an adaptogen plant, which increases the resistance to stress and causes physical vitality (5). Studies have shown that the co-therapy of patients with depression by *R. rosea* and tricyclic antidepressants induces a better antidepressant

effect than the traditional antidepressant drugs alone (19). In a randomized double-blind clinical trial, Darbinyan et al examined the antidepressant effects of *R. rosea* in patients with mild to chronic depression. Patients (90 subjects) were divided into two groups of intervention (extract at doses of 340 and 640 mg/d) and a group of placebo. The extract at both doses significantly improved the general depression as well as insomnia and emotional instability, while the placebo had no significant effects. None of the groups complained about the side effects of the medication (20). In a double-blind clinical trial study by Mao et al, the antidepressant efficacy of *R. rosea* was evaluated in comparison with sertraline. A number of 57 patients with major depression were divided into three groups of extract, sertraline and placebo. Although, the activity of the extract was lower than that of sertraline but it caused fewer adverse reactions compared to sertraline (30% versus 63%) (21). The extract of this plant shows antidepressant activity through increasing the levels of serotonin, dopamine and norepinephrine in the different parts of the brain (5, 22).

Curcumin

Curcumin is a natural chemical compound found in turmeric (*Curcuma longa* Linn). Curcumin has shown significant antidepressant effects in a large number of animal models of depression. However, its effectiveness in clinical trials is lower due to low digestive absorption (23). In a double-blind clinical trial, 60 patients with major depression were divided into three groups receiving fluoxetine (20 mg), curcumin (1000 mg) and their combination. After 6 weeks of treatment, the combination of fluoxetine and curcumin resulted in a reduction of 77.8% of the symptoms, which was higher compared to the fluoxetine (64.7%) and curcumin (62.4%) alone. In this study, curcumin was well tolerated by the patients and caused fewer side effects compared to the fluoxetine (1). In a double-blind clinical trial by Lopresti et al, the effect of daily curcumin intake was studied on patients with *major depressive disorder*. Fifty-six patients were randomly assigned to curcumin (500 mg twice daily) or placebo groups. After 4 weeks of treatment, no significant difference was found between the two groups in terms of depressive symptoms remission. However, after 8 weeks, the depressive symptoms significantly improved in the curcumin group. In addition, curcumin induced better effects in the subgroup of atypical major depression (24). In another clinical trial, forty patients with first episode of depression participated in a 5-week, double-blind, randomized, placebo-controlled study. The subjects were treated with either 500-mg/d curcumin or placebo together with antidepressants (escitalopram or venlafaxine) during August 2010 until June 2011. Result showed significant decrease in the symptoms of both groups and the patients in curcumin group showed a

better recovery. None of the patients complained about the side effects of the medications (25). Based on the reports of studies, curcumin improves the symptoms of depression by influencing the biological mechanisms involved in depression, including monoaminergic activity, inflammatory process, oxidative and nitrative pathways and activity of the HPA axis. Curcumin also increases the neurogenesis in the frontal cortex and hippocampus of mice exposed to depression (23).

Maidenhair tree or Ginkgo (*Ginkgo biloba*)

Ginkgo, from the Ginkgoaceae family, is a large and deciduous tree with fan-shaped leaves. It is an indigenous tree of China, Japan and Korea, but is now grown in many parts of the world. The seeds and leaves of the plant have been widely used in traditional Chinese medicine for the treatment of various diseases. Pharmacologically, the pure extract of the plant leaves has the potential to open arterial arteries and activate the blood circulation in the arteries, which itself provides more perfusion to the tissues. The leaf extract of the herb increases the blood flow to the brain, and thus, improves memory and intellectual ability. Currently, ginkgo is one of the most popular herbs in Germany and in the United States. In these countries, ginkgo extract is marketed under the brands of Rokan and Tanakan and is prescribed for age-related mental and physical illnesses (26). In Iran, ginkgo tablets are sold to improve and strengthen the memory (27). The antidepressant effects of ginkgo herb have been studied in a number of clinical trials. In a double-blind clinical trial, 81 patients with major depressive disorder were randomly assigned into two groups of routine electroconvulsive therapy with ginkgo pills (40 mg/8 h) and control group was treated with placebo for electroconvulsive therapy period (2 weeks). After intervention, the extract group had a better cognitive status and less depression compared with the placebo group (27). In another double-blind clinical trial, 27 patients with seasonal mood disorder were treated with ginkgo pills or placebo for 10 weeks. Based on the study results, no significant difference was found between the two groups in terms of depression score, which might be related to the small size of the samples (28). Clinical studies have also reported that the co-therapy of patients with major depression by ginkgo extract (240 mg/d) and trimipramine (200 mg) resulted in a significant reduction in the sleep disorders induced by trimipramine (29). The ginkgo extract also improves sexual dysfunctions caused by antidepressants in patients with major depression (30).

Chamomile

Chamomile dried flowers were known as an effective herbal medicine in Rome, Greece and ancient Egypt. In the traditional medicine of these countries, chamomile has been used to relieve pain, treat digestive disorders and heal

wound or injury. There are different varieties of chamomile, but two species of German chamomile (*Matricaria recutita*) and Roman chamomile (*Chamaemelum nobile*) are the most widely used species throughout the world. German chamomile has been shown to improve the symptoms of depression in animal models as well as human (6). In a double-blind clinical trial by Amsterdam et al, 57 patients with mixed anxiety and depressive disorder (MADD) were treated with placebo or chamomile capsules (220 mg/d) for 8 weeks. Nineteen patients had MADD, 16 had anxiety disorder with a history of depression, and 22 had anxiety disorder without a history of depression. After 8 weeks of treatment, the depression scores decreased significantly in the chamomile group compared to the placebo group. In addition, patients with MADD responded more strongly to chamomile than other patients (6). In another controlled trial, the consumption of chamomile tea significantly improved the quality of sleep and depression in women during the postpartum period (31). Regarding the mechanisms involved in the antidepressant effects of chamomile, it is suggested that chamomile extract and its active compounds such as apigenin and quercetin modulate norepinephrine, dopamine, serotonin, and GABA messaging, regulate the activity of hypothalamic-pituitary-adrenal axis, and inhibit monoamine oxidase enzyme activity (6). Chamomile is classified by US Food and Drug Administration as GRAS substance and its safety has been demonstrated in children, pregnant women, and people with kidney and liver diseases. Chamomile essential oil is commonly used for aromatherapy in people with sleep disorders and anxiety. Its tea is one of the most popular products which have sedative effects. Its tablets with an authorized dose of 9-15 g/d are prescribed for sedation and control of sleep disorders (32). Also, the results of recent studies on rats showed that the ethanolic extract of chamomile had a restorative effect on memory deficits and motor-coordination problems and may be useful in patients with behavioral problems. The memory enhancement effect of chamomile extract may be due to the cleansing properties of free radicals, which can be produced by the active compounds present in the extract (33).

Valerian (*Valeriana officinalis* L.)

Valerian with the scientific name of *Valeriana officinalis* L. belongs to the Caprifoliaceae family. This plant has a pleasant smell and its roots are commonly used in traditional medicine. The root of valerian has been used in Iranian traditional medicine as neurological sedative, hypnotic, anticonvulsant, antidepressant, food digester and anti-colic agent. The beneficial effects of valerian have been shown in several animal models of depression. However, few clinical studies have investigated the antidepressant effects of the plant (34). In a study, Müller et al evaluated the antidepressant effects of valerian and

St John's-wort in 2500 patients with mild to moderate depression. The treatment with St John's-wort (600 mg), valerian (100 mg), or their combination (600 mg of St John's-wort and 500 mg of valerian) significantly improved the symptoms of disease. The combination of valerian and St John's-wort showed better effects than each of them alone. Valerian and St John's-wort were well tolerated by the patients and side effects similar to the placebo were reported for them (35). In addition, the activity of valerian in improving sleep problems and general anxiety disorder have been demonstrated in clinical studies (34,36). The drug products containing valerian include valerian 1000 Herbal Relaxer, ReDormin, Safrocalm Night, and Valerian Plantapol in European countries and Neuragol-coated tablet in Iran, which are sold for relaxation effects and improving the sleep quality; however, they are not licensed by the FDA.

Lavender (*Lavandula angustifolia*)

The lavender plant, with the scientific name of *Lavandula angustifolia*, belongs to the Lamiaceae family and has long played a role in the traditional medicine. Lavender has been used in traditional medicine as analgesic, anti-spasmodic, and sedative. In clinical trials, the aromatherapy with lavender essential oil has been shown to reduce pain, anxiety, depression, and stress (37). In a double-blind clinical trial, 80 patients with mild to moderate depression were assigned to one of two groups: the case group receiving 20 mg/d of citalopram plus 5 mg of lavender twice daily and the control group receiving 20 mg citalopram twice daily. The depression symptoms were significantly lower in the case group 4 weeks and 8 weeks after the treatment. Both groups complained of dizziness and dry mouth, while no significant difference was found between them in this regard (38). In another double-blind clinical trial, 45 patients with mild to moderate depression were divided into a group receiving lavender drop (60 drops) + placebo tablet, a group receiving imipramine tablet (100 mg) + placebo drop (60 drops), and a group receiving lavender drop (60 drops) + imipramine tablet (100 mg). After 4 weeks, lavender alone caused lower antidepressant effect compared to the imipramine. The antidepressant effects of lavender and imipramine combination were significantly higher than imipramine alone. The imipramine group complained about the anticholinergic side effects such as dry mouth and urinary retention, while the lavender group complained of headache (39).

Echium amoenum

Iranian *Echium* with the scientific name of *Echium amoenum* belongs to the Boraginaceae family and exclusively grows in the Alborz Mountain Range, Iran. In Iran this plant is traditionally used to treat anxiety and to enhance mood. The anxiolytic and antidepressant

effects of *E. amoenum* have been shown in clinical studies (40, 41). In a double-blind clinical trial, 35 patients with mild to moderate depression were treated with placebo or *E. amoenum* (375 mg/d) for 6 weeks. After 4 weeks, depression was significantly reduced in the group treated with *E. amoenum*. The side effects of *E. amoenum* did not differ significantly with the placebo (41) (Table 1).

Discussion

In traditional medicine, several herbs have been recommended to cause relaxation, improve mood, and reduce sleep disorders (42). They include: *O. vulgare*, *C. asiatica*, *C. sativum*, *C. tinctorius*, *S. hortensis*, *P. ginseng*, *M. recutita*, *J. officinale*, *S. barbata*, *T. serpyllum*, *H. perforatum*, *A. graveolens*, *P. caerulea*, *V. officinalis*, *A. racemosa*, *V. officinalis*, *H. lupulus*, *I. paraguariensis*, *L. angustifolia*, *T. begonifolialinden*, *A. citrodora*, *M. officinalis*, *R. officinalis*, *T. vulgaris*, and *R. gallica*. The efficacy of some of these plants such as *H. perforatum*, *M. recutita*, *V. officinalis*, *L. angustifolia* and *E. amoenum* has been demonstrated in improving the symptoms of mild

to moderate depression in double-blind clinical trials. In addition, the antidepressant effects of *C. asiatica* (42), *C. sativum* (43), *S. hortensis* (44), *P. ginseng* (45), *C. tinctorius* (46) *A. graveolens* (47), *T. vulgaris* ((48), *P. caerulea* (49), *M. officinalis* (50), and *R. officinalis* (51) have been shown in animal models of depression, which provides further areas for research on their efficacy in the clinical studies. A review of double-blind clinical trials revealed that *H. perforatum*, *C sativus*, *M. recutita*, *V. officinalis*, *L. angustifolia*, and *E. amoenum* were effective on the symptoms of mild to moderate depression (9,18,39), while curcumin and *G. biloba* relieved the major depression symptoms (25, 29) and *H. perforatum*, exhibit antidepressant have been shown to be similar to chemical drugs (8). Some plants such as *L. angustifolia* and *E. amoenum* are effective in combination with antidepressant drugs (22,41). In addition, some like *C. sativus*, *G. biloba*, and *M. recutita* are useful in reducing the disorders such as sexual disorders and insomnia caused by chemical antidepressants drugs (7,30,32)

Clinical studies conducted on the antidepressant effects

Table 1. Medicinal plants with antidepressant activity evaluated in clinical trails

Plant	Type of study	Patients and depression type	Plant used	Method for of depression assessment	Finding	Ref.
<i>Hypericum perforatum</i>	Randomized double-blind comparative trial	149 elderly with mild or moderate depression	St. John's wort extract (800 mg) /fluoxetine	Hamilton Rating Scale	St. John's wort extract showed antidepressant effect similar to fluoxetine	(8)
	Randomized, double-blind, placebo-controlled study	332 patients with mild or moderate depression	WS® 5570 (600 or 1200 mg/d)/placebo for 6 weeks	Hamilton Rating Scale	WS® 5570 (600 or 1200 mg) showed significant antidepressant effect compared to placebo	(10)
		147 patients with mild or moderate depression	WS5573 (300 mg with a content of 0.5 or 0.5% hyperforin)/placebo for 6 weeks	Hamilton Rating Scale Depression Self-Rating Scale	WS5572 (5 % hyperforin) showed significant antidepressant effect compared to placebo	(11)
	Randomised, double blind, multicentre, parallel group trial	263 patients with moderate depression	1050 mg hypericum extract (3 times daily)/ imipramine /placebo	Hamilton Rating Scale, Clinical global impressions scale, Zung's self-rating depression scale	Hypericum extract was more effective than placebo and as effective as imipramine	(12)
<i>Crocus sativus</i> L.	Double-blind, randomised and placebo-controlled trial	Women with premenstrual syndrome	Saffron capsule (30 mg/d)/placebo for a two menstrual cycles	Hamilton Rating Scale	Extract showed significant antidepressant effect compared to placebo	(7)
	Double-blind, single-center randomized trial	40 patients with mild to moderate depression	Saffron extract (30 mg)/ fluoxetine for 6 weeks	Hamilton Rating Scale	Extract was effective similar to fluoxetine	(17)
		30 patients with major depression	Saffron capsule (30 mg)/ imipramine for 6week	Hamilton Rating Scale	Extract was effective similar to imipramine	(18)
<i>Rhodiola rosea</i>	Randomized double-blind placebo-controlled study	89 patients with mild to chronic depression	Extract (340 or 640 mg)/ placebo for 6 weeks	Beck Depression Inventory, Hamilton Rating Scale	Both doses showed significant antidepressant effect compared to placebo	(20)
	Randomized double-blind placebo-controlled study	57 patients with major depression	Extract at a dose of 300 mg/sertraline for 12 weeks	Hamilton Rating scale, Beck Depression Inventory scale, Clinical Global Impression Change	Extract was less effective than sertraline but had fewer adverse effect	(21)

Table 1. Continued

Plant	Type of study	Patients and depression type	Plant used	Method for of depression assessment	Finding	Ref.
Curcumin (<i>Curcuma longa</i> Linn)	Observer-masked trial	60 patients with major depression	Curcumin (1000 mg)/ curcumin+ fluoxetine/ fluoxetine for 6 weeks	Hamilton Depression Rating Scale	Curcumin +fluoxetine showed better effect compared to fluoxetine or curcumin	(1)
	Randomised, double-blind, placebo-controlled study	56 patients with major depression	Curcumin (500 mg)/ placebo for 8 weeks	Inventory of Depressive Symptomatology, Spielberger State-Trait Anxiety Inventory	Curcumin showed significant antidepressant effect compared to placebo	(24)
		40 patients with major depression	Curcumin (500 mg/d)/ placebo for 12 month	Clinical Global Impression-Severity Scale, Hamilton Rating Scale, Montgomery-Asberg Depression Rating Scale.	Extract was effective similar to imipramine to citalopram or venlafaxine	(25)
<i>Ginkgo biloba</i>	Randomised, double-blind, placebo-controlled study	81 patients with major depressive disorder	ECT and extract (40 mg/ 8h)/ placebo for 2 weeks	Hamilton depression questionnaire	Extract was more effective than placebo	(27)
		27 patients with seasonal mood disorder	Ginkgo pills/placebo for 10 weeks	Montgomery-Asberg Depression Rating Scale	Extract did not prevent the development of the symptoms of winter depression	(28)
Chamomile	Randomized, double-blind, placebo-controlled study	57 patients with mixed anxiety and depression disorder	Placebo/chamomile capsules (220 mg/d) for 8 weeks	Hamilton Depression Rating	Extract showed significant effect compared to placebo	(6)
	Prepost-test randomized controlled trial	80 postnatal women	Chamomile tea or placebo for 2 weeks	Edinburgh Postnatal Depression Scale	Tea showed significant effect compared to placebo	(31)
<i>Valeriana officinalis</i> L.		2500 patients mild to moderate depression	St John's-wort (600 mg)/ Valerian (100 mg)/ their combination	Hamilton Depression Rating	Combination of plants showed better effects	(35)
<i>Lavandula angustifolia</i>	Clinical trial	17 cancer hospice patients	3-percent lavender aromatherapy	11-point verbal analogs scale	Aromatherapy showed significant effect compared to control	(37)
	double-blind clinical trial	80 patients with mild to moderate depression	5 mg lavender twice daily + 20 mg/d citalopram/ citalopram for 8 weeks	Hamilton Depression Rating	Depression symptoms were significantly lower in the case group	(38)
	Double-blind, randomized trial	45 patients with mild to moderate depression	Lavender (60 drops) + placebo/ imipramine (100 mg) + placebo/ lavender (60 drops) + imipramine for 4 weeks	Hamilton Depression Rating	Lavender alone showed lower effect compared to the imipramine	(39)
<i>Echium amoenum</i>	Double-blind clinical trial	35 patients with mild to moderate depression	Placebo/Echium (375 mg/d) for 6 weeks	Hamilton Depression Rating	Echium did not differ significantly with the placebo	(41)

of medicinal plants usually have limitations such as small sample size, use of a single dose of the drug and the short treatment period. The sample size has a significant effect on the study results; if the sample size is small, it would be unlikely to achieve a significant statistical difference. In a number of studies, the antidepressant effects of medicinal plants have been compared with the placebo, while it is better to compare them with common antidepressants in addition to the placebo. The symptoms of the disease have been evaluated before and several weeks after the intervention in most clinical studies conducted on the

antidepressant effects of medicinal plants, while some herbs show their effects immediately and some show after a longer period of time. For example, in a clinical trial, curcumin had no significant antidepressant effects until 4 weeks after the treatment; but, its effect appeared from the week 4 to week 8 (24). Therefore, it is recommended to examine the symptoms in a longer treatment period on a weekly basis.

In general, pre-clinical and clinical evaluations of medicinal plants are difficult and complex. One of the major problems in this regard is the production of

standard herbal medicines with a specific and constant combination with the potential for reproduction. In general, the amount and type of chemical compounds of plants are influenced by various factors such as genetic differences, geographic area, harvest time, soil quality, plant part used, and preparation methods. Thus, the production of herbal drugs with a specific and constant compound is a difficult task. Although performing pre-clinical studies by using active ingredients of the plant seems effective but they cannot guarantee the efficacy of total extracts in the clinical studies (52).

There are several medicinal products of *H. perforatum*, *M. recutita*, and *V. officinalis* in forms of capsules, pills, and drops on the market that are prescribed for relaxation, anti-anxiety, anti-depression uses and improving the sleep problems. Before presenting the herbs in the form of drugs on the market, their safety has to be determined in numerous studies and legal approvals should be obtained from the Food and Drug Administration or similar organizations for them.

Conclusion

Some medicinal herbs have shown antidepressant effects similar to those of the conventional antidepressants in the treatment of patients with mild to moderate depression as well as the major depression. Medicinal plants do not have significant side effects in patients and the reported side effects for them are not significantly different from placebo. However, additional studies with a larger sample size are needed to confirm their antidepressant effects, adverse effects and toxicity in different individuals.

Author's contribution

MS is the single author.

Conflict of interests

The author declares that there is no conflict of interest.

Ethical considerations

The ethical issues (including plagiarism, misbehavior, data provision, forgery, duplicate release or submission, redundancy) were fully observed by the author.

Funding/Support

None.

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