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Smart Use of Herbal Drugs in the Management of Depression

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Abstract

Depression is a life-threatening chronic illness rising worldwide. Drugs used for treating depression have multiple side effects. Only 30% of patients respond adequately to the existing drugs and the remaining don't attain complete recovery. Thus, finding adequate efficacy, fewer side effects and lower costs seem to be necessary. The purpose of this study was to review "medicinal herbs" having anti-depressant properties with double-blind clinical studies. The clinical trial studies and the safety profiles of plants and their products are given to relieve symptoms of mild, moderate, or major depression and have fewer side effects than synthetic drugs.

Keywords: Depression, herbal medicines

Introduction

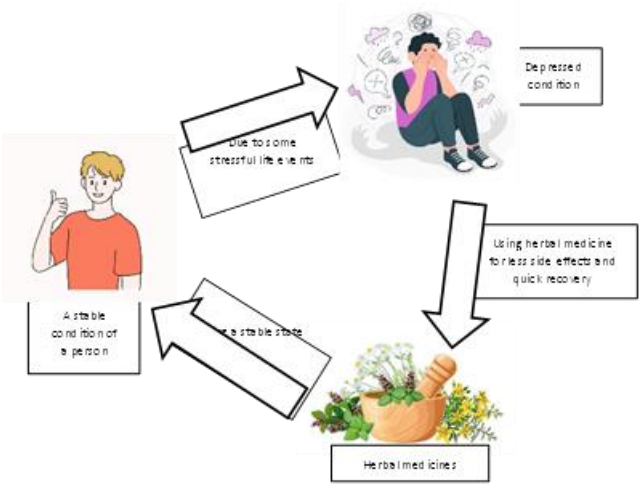
Depression is life's intimidating long-term mental condition and is increasing especially in low-income countries. Risk factors are more prevalent in these countries, i.e., poverty, unemployment, death, death of a close one, break-up, illness, mental stress, and alcohol and drug abuse.

It is a common and serious medical illness that negatively *affects our feelings, the way we think, and how we react to situations.* It is ranked fourth among the health problems according to WHO. It significantly interferes with one's ability to work, play, or have relationships. Depression increases the risk of suicide more than other mental disorders.

Some theories regarding the cause of depression tell about the lack of monoamine neurotransmitters (serotonin, dopamine, norepinephrine), decreased levels of cortisol, and dexamethasone and immune-inflammatory processes. The treatment for depression includes lifestyle modification, psychotherapy, and various drugs that decrease the reuptake of neurotransmitters and elevate their levels, which are selective serotonin reuptake

inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors.

Clinical trials show that most patients do not like to take the medication due to their side effects, therefore adequate efficacy, fewer side effects, and lower cost are one of the most important aspects for finding effective treatments for depression. That's why *medicinal plants with a wide spectrum of therapeutic properties* have attracted considerable attention as supplementary drugs or even alternative treatments for depression all over the world.



The main aim of using herbal medicines is to reduce adverse effects and the cost-effectiveness of herbal sources. Plants that have shown considerable antidepressant activities in animal studies and with fewer studies on humans are presented here.

*Hypericumperforatum*L. (St John's wort)

It is an herbaceous perennial plant of the family Hypericaceae, which is native to Western Europe, Asia, and North Africa. Several studies have been carried out on its antidepressant effects in animal models as well as human studies show that St John's wort extract was more effective than placebo and had similar to fluoxetine, and sertraline (SSRIs) and it has significantly lower side effects.

"Hyperforin" and "Hypericin" are this herb's main effective ingredients and hyperforin is a superior option to hypericin for the anti-depressant activity of the plant. It significantly inhibits the reuptake of synaptic serotonin, dopamine, and norepinephrine. The plant extract has a downregulating effect on beta-adrenergic receptors and an upregulating effect on serotonin receptors. 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-hydro phenyl glycol (MHPG)

A diagrammatic representation on working of herbal medicines

significantly increased. MHPG is a metabolite of norepinephrine degradation and is a marker for anti-depressant response.

Several pharmaceutical products prepared from Hypericum include Hypericaps, Hypericum STADA, Hypericum 300, and HypericumSyxyl S.

Saffron *(Crocus sativus* L.)

It is one of the most expensive spices in the world and belongs to the family Iridaceae. It is used as a food additive and additionally has several therapeutic effects. 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. When a randomized double-blind clinical trial took place by taking a hydroalcoholic extract of saffron and fluoxetine in mild to moderate depression patients, then after 6 weeks, saffron caused considerable improvement similar to that of fluoxetine, one of the side effects reported for saffron is an increased risk of bleeding; but in this study, saffron didn't cause abnormal bleeding. In a clinical trial, the saffron capsule at a 30mg/kg dose showed antidepressant effects similar to imipramine (100mg/kg) in patients with mild to severe depression. 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 depression.

It is proposed that two active compounds of saffron, including "Safranal" and "Crocin", inhibit the reuptake of dopamine, norepinephrine, and serotonin.

***Rhodiolarosea* L.**

It belongs to the family Crassulaceae and naturally grows in Europe, Asia, and North America.It has a long history of use for increasing physical tolerance, work productivity and longevity, enhancing energy levels, resisting high altitude sickness, and in the treatment of fatigue, depression, impotence, and infection including TB.

R. rosea is known as an adaptogen plant, which increases stress resistance and causes physical vitality. Studies have shown that co-therapy of *R. rosea* and TCAs in depression patients induces a better antidepressant effect than the traditional antidepressant drugs alone.

In a randomized double-blind clinical trial, the examination of anti-depressant effects of *R. rosea* in patients with mild to chronic depression significantly improved general depression as well as insomnia and emotional instability.

The extract of this plant shows antidepressant activity by increasing the levels of serotonin, dopamine, and norepinephrine levels in the different parts of the brain.

Curcumin

It is a natural chemical compound found in turmeric (*Curcuma longa* Linn) and has shown significant effects in a large number of animal models of depression. However, its effectiveness in clinical trials is lower due to low digestive absorption.

In the double-blind clinical trial, the combination of fluoxetine and curcumin resulted in a reduction of 77.8% in symptoms in patients with major depression. In one more clinical trial, the daily intake of curcumin (500 mg twice daily) significantly improves the symptoms of major depressive disorder after 8 weeks.

Based on the studies, curcumin improves the biological mechanisms involved in depression, including monoaminergic activity inflammatory process, oxidative and nitrative pathways, and activity of the HPA axis.

Maidenhair tree or Ginkgo *(Ginkgo biloba)*

A large and deciduous tree belonging to the family Ginkgoceae is an indigenous tree of China, Japan, and Korea, but also now grown in many parts of the world. The leaf extract of the herb increases the blood flow to the brain, and thus, improves memory and intellectual ability. It is one of the most popular herbs in Germany and the United States. Its extract is marketed under the brands *Rokan* and *Tanakan*and is prescribed for age-related mental and physical illnesses.

In a double-blind clinical trial, ginkgo pills show less depression in patients with major depressive disorder, and in another clinical trial, co-therapy of patients with major depression by ginkgo extract (240mg/d) and trimipramine (200mg) resulted in a significant reduction in the sleep disorders induced by trimipramine. The

ginkgo extract also improves sexual dysfunctions caused by antidepressants in patients with major depression.

Chamomile

Its dried flowers were known as an effective herbal medicine in Rome, Greece, and Ancient Egypt. In these countries, chamomile has been used to relieve pain, treat digestive disorders and heal wounds or injuries. German chamomile *(Matricariarecutita*) has been shown to improve the symptoms of depression in models as well as humans.

In a double-blind clinical trial, the depression scores decreased significantly in patients with mixed anxiety and depressive disorder (MADD) treated with chamomile capsules. In another controlled trial, the consumption of chamomile tea significantly improved the quality of sleep and depression in women during the postpartum period.

The essential oil of chamomile is commonly used for aromatherapy in people with sleep disorders and anxiety and when we talk about the antidepressant effects of chamomile, then it is suggested that chamomile extract and its active compounds such as "apigenin" and "quercetin" modulate norepinephrine, dopamine, serotonin, GABA messaging, and inhibit monoamine oxidase (MOA) enzyme activity. Chamomile tablets with an authorized dose of 9-15 g/d are prescribed for sedation ad control of sleep disorders. Its memory enhancement effect may be due to the cleansing properties of free radicals, which can be produced by the active compounds present in the extract.

Valerian (*Valerianaofficinalis* L.)

It belongs to the family Caprifoliaceae and has a pleasant smell.Its rhizome and roots are important pharmaceutical sourcesand are used in traditional medicine. Valerian's roots have been used in Iranian traditional medicine as a neurological sedative, hypnotic, anticonvulsant, antidepressant, food digester, and anti-colic agent.

In a clinical study, the antidepressant effects of valerian have been investigated in which patients with mild to moderate were treated with valerian (100mg), St John's-wort (600mg), or their combination (600mg of St John's-wort and 500 mg of valerian) and significantly improved the symptoms of the disease. The combination of valerian and St John's wort show better effects than each of them alone. Additionally, the activity of valerian in improving sleep problems and general anxiety disorders has been also demonstrated.

The drug product 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 sleep quality.

Lavender (*Lavandula angustifolia*)

It belongs to the family Lamiaceae and has been used in traditional medicine as an analgesic, anti-spasmodic, and sedative.

In clinical trials, aromatherapy with lavender essential oil has been shown to reduce pain, anxiety, depression, and stress. In double-blind clinical trials, patients with mild to moderate depression were assigned into two groups: one with 20mg/d of citalopram + 5mg of lavender twice daily and another one receiving only 20mg citalopram twice daily. The depression symptoms were significantly lower in the first group, but both complained of dizziness and dry mouth, while no significant difference was found between them.

Echiumamoenum

Iranian Echium belongs to the family Boraginaceae and exclusively grows in the Alborz Mountain Range, Iran. In Iran, it is traditionally used to treat anxiety and for enhancing mood.

Its anxiolytic and antidepressant properties have been shown in a double-blind clinical trial, in which patients with mild to moderate depression were treated with a placebo or *E. amoenum* (375mg/d) and the *E. amoenum* group was significantly reduce depression.

***Hops (Humuluslupulus* L.)**

It is the most important and known species of *Humulus*, a perennial and dioecious climbing plant. It is native to central Europe and is industrially grown throughout the temperate regions of the North. A subject of scientific and industrial interest is “female inflorescences” (cones) which contain essential oil, triterpenes, flavonols, and tannins. It is a basic source for the brewing of beer and also for herbal preparations. These preparations are characterized as “traditional herbal medicinal products”, which can be used for the relief of mild symptoms of mental stress and to aid sleep.

A double-blind clinical trial is performed with a placebo or capsules (food supplement), and two capsules of dry hop extract (0.2g, once daily in the evening). Symptoms are evaluated in all study participants and a

significant decrease in anxiety, depression, and stress was observed with both hops and placebo, which was greater with hops compared to placebo.

In this study, clinical trials of better quality are needed to determine the effect of hops on the CNS.

Aloysiatriphylla

Aloysiatriphylla (lemon verbena) is a perennial medicinal plant, belonging to the family Verbenaceae and native to western South America. It is having two flavonoid compounds that show therapeutic effects, which are – "Hesperidin" and "Artemitin". It is having some therapeutic properties that, it is being used in depression from early times, is an antioxidant, has a tonic effect on the nervous system, and has a reputation for soothing abdominal discomfort.

Citrus aurantium

Citrus aurantium (sour orange) belongs to the family Rosacea and it has been used in traditional medicine for its therapeutic effects like antidepressants, antianxiety, and anticonvulsants due to its effect on CNS. Some clinical studies reported that its essential oil has affected anxiety and depression and can be a good alternative to chemical drugs.

Melissa officinalis

Melissa officinalis (lemon balm) belongs to the family Lamiaceae is native to Western Asia and Eastern Mediterranean and is also known as "Badranjboyeh" in Iran. Its aerial parts are used in traditional medicine and show different therapeutic effects such as carminative, antidepressant, anti-anxiety, surgical dressing for wounds, sedative, hypnotic, diuretic, antispasmodic, and as well as in nerve-calming. In Iranian folk medicine, the using of Melissa officinalis used for nervousness, depression, and lack of energy in young girls.

Salix aegyptiaca

Salix aegyptiaca (Musk Willow) belongs to the family Salicaceae, it is native to Southwest Asia and is also found in some areas of Iran. Flowers of this plant show therapeutic properties which are separated into different male and female flowers in different plants. In Iranian traditional medicine, the male flower distillate has been used to treat depression, anemia, vertigo, as well as cardiovascular problems.

Viola odorata

Viola odorata (Sweet violet) belongs to the family Violaceae, it is native to Asia, and Europe and was also introduced to North America and Australia. Flowers of violet have been used as an antidepressant, anti-insomnia, laxative, lipid-lowering, anti-inflammatory, blood pressure lowering, and anti-septic treatment. Recent studies show that the main compounds of violet leaves which are glucosides of salicylic acid have been used to treat body pains and headaches.

Cinnamomum verum

Cinnamomum verum (cinnamon) belongs to the family Lauraceae, it is native to Sri Lanka and has a lot of therapeutic effects such as antidepressants, anti-microbial, antioxidant, and anti-viral. Some studies show that it can reduce the risks of colon cancer by Improving the colon's health.

Camellia sinensis

Camellia sinensis (Green tea) belongs to the family Theaceae and has shown anticancer, antifibrotic properties, and anti-neurodegenerative activities. Recently, a preclinical study demonstrated that a compound obtained from Camellia sinensis which is "polyphenols" (5, 10, and 20mg/kg PO for 7 days) improves depression-like behavior and decreased the serum level of corticosterone.

A table representing herbal medicines used for Depression: -

Herbal medicines	**Family**	**Growing areas**	**Chemical constituents**	**Uses**
St John's wort *(Hypericumperforatum*L.*)*	Hypericaceae	Western Europe, Asia, and North Africa	Hyperforin and hypericin	As an antidepressant, phytochemicals, and dietary supplement
Saffron *(Crocus sativus* L.*)*	Iridaceae	Grows in a belt from Spain in the west to India in the east. Iran is responsible for almost 45% of its global production	Safranal	used in traditional medicine as an antispasmodic, analgesic, anti-inflammatory, sedative, carminative, sweat enhancer, expectorant, stimulant, gastric strengthener, sexual desires stimulant, and as an agent to develop early menstruation.
Rhodiolarosea L.	Crassulaceae	Europe, Asia, and North America	Rosin and its derivatives, salidroside	Provides an anti-fatigue effect, is used in mild to moderate depression, and generalized anxiety
Turmeric (*Curcuma longa*)	Zigiberaceae	Native to southern India and Indonesia	Curcumin	Antibacterial, anti-inflammatory,

				antioxidant, wound-healing, and antimicrobial activities
Maidenhair tree or Ginkgo *(Ginkgo biloba)*	Ginkgoceae	China, Japan, and Korea	Ginkgolides and bilobalide	Used to treat brain, circulatory, and respiratory conditions and also for depression
Chamomile	Asteraceae	Rome, Greece, and Ancient Egypt	Apigenin, chamazulene	used to relieve pain, treat digestive disorders and heal wounds or injuries
Valerian (*Valerianaofficinalis* L.)	Caprifoliaceae	England, France, Belgium, Holland, Germany, eastern Europe, and Japan	Actinidine, creatinine	As a sleep aid and as a sedative for nervous tension, hysteria, excitability, stress, and intestinal cramps
Lavender *(Lavandula angustifolia*)	Lamiaceae	Italy, France, Spain	Linalool, eucalyptol, linalyl acetate	As an analgesic, anti-spasmodic, and sedative
Echiumamoenum	Boraginaceae	The northern part of Iran, Caucasus, and Russia	Rosamarinic acid, anthocyanidins, flavonoids	As a demulcent, anti-inflammatory, analgesic, especially for the common cold, and as an anxiolytic and sedative
Hops (Humuluslupulus L.)	Cannabaceae	Southwest England and the United States	Alpha acids and beta acids	Used for anxiety, insomnia, and other sleep disorders, restlessness, tension, nervousness, and irritability
Aloysiatriphylla	Verbenaceae	Argentina, Uruguay, Chile, and southern Brazil	Spathulenol, citral	Used in indigestion, diarrhea, and constipation and also in insomnia, anxiety, and heart problems
Citrus aurantium	Rosacea	Southern Asia	Synephrine, terpineol, ocimene	As a stimulant and appetite suppressant, flavoring and acidifying agent
Melissa officinalis	Lamiaceae	South-central Europe, Basin, Iran, and Central Asia	Citronellal, citral, geraniol	Reduce stress and anxiety, promote sleep, improve appetite, ease pain and discomfort from indigestion
Salix aegyptiaca	Salicaceae	Egypt, Iraq, Afghanistan, and Pakistan	Gallic acid, caffeic acid, myricetin, catechin, salicin	Treatment of chronic and acute inflammation, infection, pain, and fever
Viola odorata	Violaceae	Europe, Central Russia, North Africa	Alkaloids, flavonoids, glycosides, tannins, and terpenes	Used to treat insomnia, cough, fever, common cold, and bronchitis
Cinnamomum verum	Lauraceae	Sri Lanka, Indonesia, Chin, and Vietnam	Eugenol, cinnamyl acetate, and cinnamaldehyde	Anti-diabetic, antibacterial, antioxidant, anti-

				inflammatory, and anticancer effects
Camellia sinensis	Theaceae	India, China, Japan, and Sri Lanka	Catechins, polysaccharides, proteins, saponins	Improve blood pressure dysfunction and restore antioxidant enzyme activity
Ashwagandha (*Withaniasomnifera)*	Solanaceae	India, the Middle East, and parts of Africa	Withanolide and withaferin	Relieves stress and Anxiety, lowers blood pressure, sharpens focus and memory
Maca root *(Lepidiummeyenii)*	Brassicaceae	Peru, in the high Andes of Bolivia and to a small extent of Brazil	Leucine, Arginine, phenylalanine, lysine	Used to manage stress, help with depression, lead to increased energy
Rosemary *(Rosmarinusofficianalis)*	Lamiaceae	Tunisia, Morocco, and Spain	Eucalyptol, carnosol	Boost immune and circulatory systems, improve memory, and alleviate muscle pain
Green tea (*Camellia sinensis)*	Theaceae	China, India, Sri Lanka, Kenya	Catechins, caffeine, chlorogenic acid, gallic acid	Control bleeding and heal wounds, aid digestion, improve heart and mental health, and regulate body temperature
Kavakava*(Piper methysticum)*	Piperaceae	Vanuatu, Fiji, Papua New Guinea, Samoa, Hawaii	Kavain, methysticin	Treat anxiety, insomnia, elevate mood, wellbeing and produce a feeling of relaxation
Brahmi*(Bacopamonnieri)*	Scrophularaciae	India, Nepal, Sri Lanka, China, Pakistan, Taiwan, Vietnam	Bacoside, bacopaside	Used for Alzheimer's disease, improving memory, anxiety, attention deficit hyperactivity disorder (ADHD)

DISCUSSION

The efficacy of some plants such as *H. perforatum*, *V. officinalis* L., and *E. amoenum*has been demonstrated in improving the symptoms of mild to moderate depression in double-blind clinical trials. A review of double-bind clinician trials also revealed that curcumin and *G. biloba* relieved major depression symptoms and *H. perforatum*, exhibited antidepressant activity to be similar to chemical drugs.

Pre-clinical and clinical evaluation of medicinal herbs is 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. The amount and type of chemical compounds in plants are influenced by various factors which include

genetic differences, geographic area, harvest time, soil quality, plant part used, and the preparation methods. Even though performing pre-clinical studies using active ingredients of the plant seems effective, they cannot guarantee the efficacy of total extracts in the clinical studies.

An important point regarding these medicinal herbs for presenting drugs on the market is that their safety has to be determined in numerous studies and legal approvals should be obtained from the FDA or similar organizations for them.

Conclusion

Several phytochemicals and medicinal herbs with in vivo and in vitro results have still not been investigated in humans and in vitro and in vivo studies are also needed to discover details about the anti-depressive mechanisms of medicinal herbs.More studies are needed to validate the mechanism of action and identify the compounds responsible for the effects of medicinal herbs.

References

1. "Journal of herbal pharmacology" (JHP); Medicinal herbs with anti-depressant effects.
2. Medicinal plants used for anxiety, depression, or stress treatment: An update.
3. "Ingenta connect"; Herbal Approaches in the Management of Mental Depression.
4. Herbal medicines, other than St. John's wort, in the treatment of depression: a systematic review.
5. "Journal of Applied Pharmacy"; Review article on "Phyto-Pharmacological effect of Nine Medicinal Plants as a Traditional treatment on depression".
6. Hindawi; "Therapeutic effects of phytochemicals and medicinal herbs on depression".
7. Herbal medicine for Depression and Anxiety: A systematic review with Assessment of Potential Psycho-Oncologic Relevance; HHS Public Access.
8. A naturalistic study of herbal medicine for self-reported depression and/or anxiety a protocol; Integrative Medicine Research.
9. Review of Herbal Medicines for the Treatment of Depression; Natural Product Communication.
10. Depression and Treatment with Effective Herbs; ResearchGate.
11. Herbal Medicine in the Treatment of Depression and Anxiety; Journal of Medicinal Plants.

12. Chinese Herbal Medicine in the Treatment of Depression in Parkinson's disease: From Molecules to Systems; Frontiers in Pharmacology.
13. Management of Depression and Uses of Natural Medicine; Genera Medicine: Open Access.
14. A review of Herbal Medicines for Psychiatric Disorders.
15. Medicinal plants in the Treatment of Depression. II: Evidence from Clinical Trials.