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Phyto-Pharmacological Effects of Medicinal Plants for the Treatment of Depression

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Abstract

Background: Depression is a serious mental illness that has a significant impact on suicidal thoughts. It is ranked as the fourth most significant mental disability globally. Current research is concentrating on increasing the effectiveness of conventional treatments due to highly undesirable effects. Natural goods, herbal plants, and phytochemicals offer a wide range of study opportunities for antidepressant treatments.

Objective: The present study aim at the review of various photo-Pharmacological effects of medicinal plants for the treatment of depression in a traditional approach

Methods: The methodology includes a thorough search of every electronic source to gather all information on herbal plants, pharmacological effects, and antidepressant mechanisms of phytochemicals from the year 2000 to 2023.

Results: Different plant metabolites were shown to have powerful antidepressant effects, including polyphenols (phenolic acids, flavonoids, lignans, and coumarins), alkaloids, terpenes and terpenoids, saponins and sapogenins. Major group of phytochemicals crucial in evaluating antidepressant effectiveness includes piperine, diterpene alkaloids, berberine, hyperforin, riparin derivatives, ginsenosides, and -carboline alkaloids. A great inhibitor of monoamine oxidase enzymes, an elevation in brain 5-HT and BDNF (Brain-Derived Nicotinic Factor) levels and modulatory effects on the hypothalamus-pituitary-adrenal axis were all demonstrated by piperine. Numerous studies have demonstrated berberine's serotonergic, noradrenergic, and dopaminergic effects, demonstrating the importance of phytochemicals from various sources in the treatment of depression.

Conclusion: All of the medicinal plants listed in this study's thorough review indicated the ability to cure depression using various traditional methods and a variety of processes. In order to discover potential natural, semi-synthetic, or synthetic antidepressants with fewer side effects, the structure-activity

relationship of extremely effective antidepressant phytochemicals was evaluated. For verification of natural antidepressant effectiveness and fulfilment of their safety profile, more clinical investigations are also required.

Keywords: Antidepressant effect, depression, medicinal plants, phytoconstituents, pharmacological effect.

INTRODUCTION

The use of medicinal plants and their extracts as natural treatments for illnesses like depression and anxiety is wonderful and has great promise. Numerous herbs have been used to treat depression in traditional medicine for many years. Through invivo studies, various plant extracts and natural products have been evaluated as possible antidepressant agents (1). Dopamine, serotonin, and noradrenaline are the main neurotransmitters involved. The majority of these studies concentrate on the potential mediators implicated in these potential effects. There are over 650 reports of medicinal plants that resemble antidepressants in PubMed; 155 of them have been included in this review, together with a pertinent group of researchers.The most pertinent species investigated in both preclinical and clinical investigations are saffron and turmeric; St. John's wort has also undergone significant testing. To the best of our knowledge, no review has yet offered a thorough comprehension of the bio molecular mechanisms by which these herbs function or whether their possible effects might be advantageous (2). To examine the therapeutic potential of these plants that resemble antidepressants and help develop new therapeutic approaches to lessen the enormous burden that depression places on people all over the world, the narrative review's goal is to provide an update on medicinal plants from the year 2000 to the present.

TYPES OF DEPRESSION:

Depressive sickness comes in numerous forms, even as several different illnesses:
• **Major depression** is manifested by a combination of symptoms that interfere with the ability to work, sleep, eat, and luxuriate in once-pleasant activities. These disabling episodes of depression will occur once, double, or many times in a very period.
• **Dysthymia**, a less severe kind of depression involves long, chronic symptoms that don't disable, but keep you from working at “full steam” or from feeling sensible. Generally, folks with dysthymic depression conjointly expertise major depressive episodes
•**Manic-depressive or bipolar** isn't nearly as current as different varieties of depressive sicknesses. It involves cycles of depression and elation or mania. Generally, the mood switches are dramatic and speedy; however, most frequently they're gradual. Once within the depressed cycle, one will have any or all different symptoms of a depressive sickness. Once within the wild cycle, any or all symptoms listed beneath mania could also be fully fledged. Mania typically affects thinking, judgment, and social behaviour in ways which could cause serious issues and embarrassment (3).

NEUROCHEMISTRY OF DEPRESSION

The monoamine hypothesis is currently the main area of study in the domains of pathophysiology and pharmacotherapy. Many of the antidepressant targets were based only on this idea, which would have an effect lasting over 25 years (4). According to this notion, serotonin, norepinephrine, and/or dopamine levels in the brain are out of balance and decreasing. Serotonin, also known as 5-hydroxytryptamine (5-HT), is one of the three main neurotransmitters in the brain and is crucial in the development of depression and mood swings. The other two neurotransmitters are norepinephrine and dopamine. The raphe nucleus of the brain contains serotonin binding sites. These locations include the limbic system, frontal cortex, and striatum, which have an impact on the hippocampus and hypothalamus. Serotonin regulates a variety of emotions and behaviors, including those related to appetite, impulsivity, aggressiveness, anxiety, and fear. Norepinephrine encourages vigilante behavior by raising arousal and attentiveness. Additionally, it improves memory storage and retrieval(5). Dopamine primarily regulates motivated behaviour, the release of various hormones, and motor coordination.

PHYTO-PHARMACOLOGICAL EFFECTS OF MEDICINAL PLANTS

1. ***Aloysia triphylla*** **(Verbenaceae)**is a bushy, perennial plant that was first domesticated in South America and is now grown throughout the Middle East. Traditional medicine has long employed *Aloysia triphylla*. According to reports, Aloysia triphylla has a mild calming effect and combats depression (6). The plant is known for relieving abdominal pain and has a tonic impact on the nervous system. The plant has been discovered to have antioxidant properties. Artemitin and hesperidin have been isolated through phytochemical analysis of *Aloysia triphylla's* aerial parts. It has been asserted that artemitin possesses anti-inflammatory properties. Additionally, it was discovered that artemitin causes smooth muscle to relax. A bioflavonoid known as hesperidin has been found to have a variety of pharmacological effects, such as inhibition of histamine release; and inhibition of eicosanoid synthesis(6,7). Additionally, hesperidin was found to have central nervous system depressant effects.

2. Lavandula angustifoliaAn essential herb with a long history in traditional medicine and ongoing therapeutic usage is lavender. This plant's fresh flowering tops, which yield an essential oil, are frequently used in aromatherapy as a sedative. Studies on both humans and animals have demonstrated sedative effects from inhaling the vapour of lavender essential oil, which contains linalool as its primary component. There have also been reports of other pharmacological properties of this oil, including anticonvulsive, anxiolytic, antidepressant, and anticonflict effects(8). However, aqueous extracts of lavender are also used as a tea infusion to treat neurological diseases of the stomach and intestines, sleeplessness, and restlessness. Aqueous phenolic components including hydroxycinnamic acids and flavone glycosides are also present in lavender.

3. Cinnamomum zeylanicumNumerous positive health effects of cinnamon and its extract include antibacterial, antiviral, antioxidant, and antidepressant properties. Cinnamaldehyde, a key component of the essential oil responsible for the flavour and scent of whole cinnamon, may be responsible for many of the corresponding bioactivities. Additionally, the aqueous extract contains many polymeric polyphenol compounds called proanthocyanidins, which are most likely in charge of the majority of the antioxidant effects of cinnamon(10). Proanthocyanidins have other qualities that may be crucial for their bioactivities, despite the fact that the health-promoting benefits of bioflavanoids in general are often assumed to be caused by their antioxidant activity. Procyanidins and catechins are found in cinnamon bark. Both procyanidin A-type and B-type links are procyanidins' constituents. These procyanidins that are derived from berries and cinnamon have antioxidant properties as well. Additionally, cinnamon can enhance colon health, lowering the risk of colon cancer. Cinnamon acts as a coagulant to stop bleeding(11). Cinnamon also speeds up tissue regeneration and improves uterine blood circulation. Aside from its crucial function as a spice, this plant's essential oils and other components also have significant antidepressant, antibacterial, antifungal, antioxidant, anti-diabetic, and anti-inflammatory properties.

4. Salix aegyptiaca usually referred to as Musk In various Iranian areas; willow is a blooming plant that is typically grown as a hedge and for ornamental purposes. One plant only exhibits one sex; however it has both male and female flowers. Bees pollinate seeds, which are needed for growth and are either male or female. Iranian folk medicine has historically utilised the plant's male inflorescence distillate as a fragrance addition, cardiotonic, and treatment for anaemia, vertigo, and depression(12). Gallic acid, caffeic acid, vanillin, p-coumaric acid, myricetin, catechin, epigallocatechin gallate, rutin, quercetin, and salicin were all detected as phenolic components in the extracts. These inflorescences' aqueous extract and essential oil are also used to make confections, tasty syrups, and most notably a regional confectionery called Noghl-e Urmia. Additionally, S. aegyptiaca has a variety of therapeutic uses, including laxative, cardioprotective, nervous, sedative, hypnotic, somnolent, aphrodisiac, orexigenic, carminative, and gastroprotective. As a nervonic functional food, S. aegyptiaca leaves decoction in honey is still used(13).

5. Grape with the scientific name ***Vitis vinifera*** having a scientific name the family Vitaceae includes the genus *Vitis vinifera*. Due to its antioxidant properties and stimulation of neurotrophic factor secretion, grape seed extract, as demonstrated in another study, lessens the damaging effects of brain ischemia in rats. This is because antidepressants can exert their effects by increasing norepinephrine, serotonin, and brain-derived neurotrophic factors. Thus, grape seed extract has the potential to be anti-depressant (14). According to research, grape seed oil can lower male rats' anxiety levels by preventing oxidative stress in a high cross-maze paradigm. Grape seed extract can therefore be used to treat anxiety disorders because it is highly rich in antioxidant chemicals including cyanidine prostaglandin. According to research, the flakonoid chemicals in

the extract of mozzarella grape kernels lower anxiety levels in a cross-legged maze test. This is likely accomplished by activating GABA receptors and raising serotonin secretion (15).

6. Hypericumhaving scientific name Antioxidant properties of the herb Hypericum perforatum have been established. Hypericum has an active ingredient called hypericin and hyperforin that inhibits the monoamine oxidase enzyme and increases serotonin levels in the diencephalon region of the brain, as well as compounds that are agonists of GABA and sigma opioid receptors, which are how it exerts its antidepressant and anti-anxiety effects(16). Similar to the chemical antidepressant effects of imipramine medicine, the hypericum molecule found in hypericum extract exhibits anti-depressant and anti-anxiety properties. According to a study on the impact of herb extract on students' anxiety in dorms in Karaj, this plant can help these students feel less anxious.in these students and due to the absence of side effects of this herb extract it is recommended in the treatment of anxiety(17).

7. Artemisia dracunculus *L.* belongs to the Compositae family, which having compounds such as monoterpene, sesquiterpene, estragole, ocimene and methyl chaviacol has antioxidant, anti-diabetic, antibacterial and antiinflammatory properties. Tarragon contains several bioactive elements such as flavonoids (flavones, flavanones, dihydro flavanols, and chalcones, and phenolic acids (hydroxybenzoic, caffeic, or 5-Ocaffeoylquinic acids, among others) as well as a small amount of vitamin and sesquiterpenoids(17,18). The most important aromatic compounds of this plant are methyl eugenol, c, and thymol. Anticoagulation, anti-fungal, anticonvulsant, analgesic as well as liver and stomach protecting effects of tarragon have been proven. The hydro-alcoholic extract of tarragon extract, probably due to its antioxidant compounds, reduces anxiety and depression in rats exposed to chronic restraint stress. 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 antianxiety 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(19). Carvacrol reduces depression by affecting the dopaminergic (and not noradrenergic or serotonergic) system.

8. ***Brahmi (Bacopa monnieri***) Brahmi (Bacopa monnieri) (Family Scrophulariaceae) is a small creeping herb found throughout India in marshy grounds. The stem and leaves are used for several medicinal purposes. Traditionally it has been used in Ayurveda as a rasayana (medhya-rasayana and aindra-rasayana) to rejuvenate the brain and mental health and promote intellect, memory, and longevity. 49 It showed nootropic and cholinergic properties and has therefore attracted attention for its potential to treat neurodegenerative disorders(20). 50-58 Several studies have also demonstrated the anti-depressant activity of B. monnieri at the dose of 20 and 40 mg/kg in the forced swim, tail suspension, chronic unpredictable stress, and learned helplessness models using mice and rats.
Due to the presence of sapononins - bacopasides VI-VIII, bacopaside I, bacopaside II, and bacopasaponsin C in B. monnieri. 59-61 recent clinical study have proved a polyherbal formulation consisting of B. monnieri, D. bulbifera, and H. rhamnoides was also found to improve cognitive performance and lower depression scores in both demented and non-demented elderly(21).

9. ***Curcuma longa (Haridra)*** Traditionally, *Curcuma longa* is also known as Haridra or Haldi or turmeric in India, belongs to the family Zingiberaceae. It contains the active phytochemical such as alkaloid – curcumin which possesses a range of pharmacological properties-anti-inflammatory, anti-oxidant, antimicrobial, anti-carcinogenic, anti-diabetic, and neuroprotective activities. 64,65 Recent studies have also demonstrated the anti-depressant activity in mice using the TST and FST which was of greater potency than fluoxetine(22).

10. Oenothera biennisLinnbelongs to the family Omnagraceae and the cultivated in the UK. Its seeds are used for isolating fixed oil known as evening Primerose oil. Evening Primerose oil at doses of 0.2 ml/20 g showed significant antidepressant action in a mouse model of chronic fatigue syndrome (CFS) in which mice were forced to swim every day for 7 days for 6 minutes sessions (23).

11. ***Viola odorata****Viola odorata* is aspecies of the genus Viola belong to its native country Europe and Asia, but has also been introduced to North America and Australasia. It is commonly known as wood violet, sweet

violet, English violet, common violet, or garden violet. The sweet scent of this flower has proved popular throughout the generations, particularly in the late Victorian period, and has consequently been used in the production of many cosmetic fragrances and perfumes(24). In the traditional system, it has been used for anxiety, insomnia and to lower blood pressure. Violet is mainly used as an herbal remedy in cases of various respiratory ailments(25). It can be very beneficial in the treatment of congestion, coughs and sore throat. Recent studies have shown the presence of glycoside of salicylic acid in Common Violet leaves, which explains its efficient use in cases of headaches and body pains(26). Syrup made from Common Violet's flower has anti-septic, anti-inflammatory, laxative and expectorant properties. It can be helpful in cases of various respiratory conditions, but also in the treatment of headaches, insomnia, dizziness and exhaustion(27). Viola contains alkaloids, glycoside, saponins, methyl salicylate, mucilage and vitamin C. The plant has been reported to possess antioxidant and diuretic activities along with other beneficial effects but no study has been found regarding its blood pressure lowering or lipid-lowering activity.

12. ***Cimicifuga racemosa*** L. (Nutt.) Black cohosh regulatory bodies have included the use of *C. racemosa* L. (Nutt.) for depressive mood swings among other indications. Several studies on *C. racemosa* (black cohosh) have reported its application for menopause-related anxiety disorder. The standard extract of *C. racemosa* contains triterpene glycosides (cimicifugoside, 23-epi-26-deoxyactein and actein), aromatic acids (salicylic acid and ferulic acid), tannins, resins, phytosterols and fatty acids. Recently, Nx-methylserotonin was identified in the roots/rhizomes of C. racemosa as a potent agonist of serotonin 5-HT1A and 5-HT7 receptors(28). Despite the extensive use of C. racemosa especially during menopause, clinical studies did not show significant anxiolytic effect of black cohosh as compared to placebo. The small sample size, choice of black cohosh preparation and dose used may have been the limiting factors in these studies(29).

13. ***Passiflora incarnata L***. (Passion flower) the herbal medicines derived from *P. incarnata* are prescribed in many parts of the world to treat some CNS disorders. This plant is used for the treatment of insomnia and anxiety disorders in Brazil, Europe and USA. Clinical applications of this species worldwide have led to its inclusion in British Herbal Pharmacopoeia (1983), Homoeopathic Pharmacopoeia of India (1974), United States Homoeopathic Pharmacopoeia (1981), Pharmacopoeia Helvetica (1987), and in the pharmacopoeia of Egypt, France, Germany and Switzerland (30). Phytochemical studies of P. incarnata showed the presence of flavonoids (orientin, isoorientin, vitexin, isovitexin and chrysin), cyanogenic glycosides and indole alkaloids(31). Zanoli *et.al*and Brown *et al*. reported the anxiolytic-like effect of chrysin in rats, which might be due a benzodiazepine receptors ligand(32). However, the anxiolytic effects of P. incarnata do not seem to be associated solely chrysin or another compound, but it seems associated with phytocomplex (different phytoconstituents) acting in a synergistic manner (33).

14. ***Acanthopanax senticosus,*** also called 'Ciwujia' and 'Siberian ginseng' is a small shrub. Its height is approximately 1.5 to 2.6 m high. It belongs to the native to the northeastern region of China, Korea, and Japan, as well as the far-eastern region of Russia (34). It is a widely used medicinal herb with a lot of medicinal uses. It belongs to the family of Araliaceae and is known as a powerful tonic herb with lot of health benefits(35). In China, Japan and Russia, for mental and emotional problems, root bark extract of *A. senticosus* has been known for thousands of years to reduce stress and emotional problems (36). It is also used as a medication to reduce stress. It is among the ten most popular supplements used in the United States and also listed in Chinese Pharmacopoeia for its high medicinal value(37). However, little is known about the antidepressant effects of *A. senticosus*. Therefore, the present study aimed to explore the anti-depressant effects of *A. senticosus* extract (ASE) at doses of 500, 1000, and 2000 mg/kg using the forced swimming and tail suspension tests with mice(38,39). We also investigated the probable mechanisms of action for the anti-depressant effects by analyzing monoamine neurotransmitters including 5-hydroxytrylamine (5-HT), norepinephrine (NE), and dopamine (DA), as well as cAMP response element-binding (CREB) protein in the whole brain of mice following ASE treatment (40).

15. ***Withania somnifera*** In Ayurveda, the roots of *Withania somnifera* (Ashwagandha) is believed to possess aphrodisiac, sedative, rejuvenative and life prolonging properties. It is traditionally used to treat the following symptoms and conditions, although there are few scientific studies on the health benefits of Ashwagandha(40). Although Ashwagandha is effective in the treatment of chronic fatigue, nervous exhaustion, memory loss5, 6 and neurodegenerative disorders 7 only a few studies are there with the evidence of health benefits of Ashwagandha(39,40). *Withania somnifera* grows as a short shrub (35-75 cm) with a central stem from which branches extend radially in a star-like pattern (stellate) and covered with a

dense matte of wooly hairs (tomentose). The flowers are small and green, while the ripe fruit is orange-red and has milk-coagulating properties. The plant also has long brown tuberous roots that are used for medicinal purposes(36). It is cultivated in many of the drier regions of India such as Manasa, Neemuch, and Jawad tehsils of the Mandsaur District of Madhya Pradesh, Punjab, Sind, and Rajasthan. The properties of AGG can be studied with various extracts; however, the traditional usage of herbs has shown that its CNS activity will be better when administered along with ghee or honey(37). Hence, the present study in order to see the effect of Ashwagandha, its grutha (fat) extract was considered (41). Specific objectives of the study were:
a) To evaluate the antidepressant activity of Ashwagandha
b) To compare the anti-depressant activity of Imipramine, Ashwagandha, and their combination in experimental mice(42)

CONCLUSION

Numerous medicinal plants and the phytochemicals they contain have been examined and researched for the treatment of depression. Numerous medications are being developed and examined for their pharmacological and toxicological effectiveness, which are showing promising outcomes even in clinical trials. In order to determine the therapeutic usage to treat depression, various medicinal plants were gathered for this review, and their phytochemicals were described using traditional methods. It was discovered that many phytochemicals could act as lead molecule for upcoming pharmacological studies. The efficacy of several plants for treating depression has been collectively examined and documented with regard to receptor-based tests, transporter-inhibition assays, and monoamine oxidase-inhibition-based investigations. However, more research on in-vivo and animal studies is required to prove that the specific plant has the strength and effectiveness of its phytochemicals to act as an antidepressant. Animal studies include a variety of screening techniques and are specifically designed to have superior pharmacological effects on various mechanisms, either by blocking or inhibiting depressive enzymes.

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