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Herbal Medication and Natural Products in The Management of Mild To Moderate Depression: A Critical Review of Phytochemical and Pharmacological Properties.

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Abstract:

Depression is a common mental health disorder that significantly contributes to the global disease burden and ranks among the leading causes of disability worldwide. Due to the limitations of conventional antidepressant treatments, which often include adverse effects, complementary therapies are essential. These alternative approaches can alleviate symptoms of depression and help prevent relapse. Recently, herbal medications have gained considerable attention as they tend to have fewer side effects and are more cost-effective compared to other depression treatments.Consequently, leading pharmaceutical companies are actively investigating plant materials for their potential therapeutic benefits. Depression is linked to reduced levels of monoamines, including noradrenaline, dopamine, and serotonin in the brain. Thus, therapies aimed at restoring these diminished monoamine levels by inhibiting monoamine oxidase or reducing the reuptake of these neurotransmitters may prove advantageous in treating depression. This review emphasizes medicinal plants and plant-derived formulations that have demonstrated antidepressant effects in both animal and human research.

Keywords: Herbal medicines, Depression, Phytochemicals, herbs.

Introduction

Depression

Millions of individuals worldwide suffer from depression, a common mental illness. It can affect both personal and professional life by causing mental distress, loss of interest in everyday tasks, and chronic unhappiness. Even if traditional therapies like therapy and antidepressants work, some people may not be able to afford them or experience negative side effects. Consequently, a lot of people use natural goods and herbal pharmaceuticals as supplemental or alternative therapies. A persistently low mood and diminished interest in activities are hallmarks of depression, a mental health illness. It can negatively effect an individual's cognitive abilities, habits, attitudes, emotional well-being, and general health, and it has been acknowledged as a major health concern worldwide. Depression involves a number of brain diseases with distinct underlying causes, marked by a wide spectrum of symptoms reflecting variations in cognitive, psychomotor, and affective processes. The global prevalence of depression is still strikingly high and is connected with considerable levels of sickness and death. The World Health Organization estimates that around 121 million individuals globally are affected by clinical depression.[1,2].

Depression will rank as the second most common cause of long-term impairment by 2020, and by 2030, it is expected to overtake all other causes, according to the World Health Organization's Global Burden of Disease study. [3] Forty-five percent of all disability-adjusted life years associated with mental health problems are caused by depression, a prevalent neuropsychiatric illness. The symptoms of major depressive disorder include decreased interest, trouble sleeping, lack of appetite, and chronic melancholy; on the other hand, it can also manifest as restlessness and increased hunger. Drugs (pharmacological therapies), counseling (such cognitive behavioral therapy and interpersonal therapy), and electroconvulsive therapy are all options for treating depression.Using phytochemicals and medicinal plants that have few adverse effects and have therapeutic results might be an alternate strategy. [4] There are both bodily and emotional symptoms that can accompany depression. Reduced libido, sleep difficulties, decreased appetite, and slower thinking and movement are examples of biological causes. Along with poor self-esteem characterized by feelings of shame, inadequacy, and unattractiveness, people may experience emotional difficulties making decisions and a decline in motivation. They may also experience profound melancholy, indifference, and a gloomy outlook on life.[5]Genetic factors may be the primary cause of depression. This can be shown in family patterns, especially in research including twins or adopted persons. About 30 to 40 percent of instances of depression are caused by genetic factors. Conversely, 60–70% of the condition is caused by non-genetic factors. People between the ages of 15 and 45 are impacted by these non-genetic variables, which are mostly socioeconomic. Marital issues, divorce, long-term trauma, a lack of social support, relational problems, childhood sexual abuse, and the death of a loved one are all significant factors.[6]

Traditional pharmacological treatments for depression fall into three broad categories: tricyclic antidepressants, second-generation antidepressants, and monoamine oxidase (MAO) inhibitors. MAO inhibitors function by preventing the monoamine oxidase enzyme family from becoming active. The first line of therapy is frequently recommended MAO inhibitors, such as moclobemide, phenelzine, isocarboxazid, and tranylcypromine. By preventing norepinephrine and serotonin from being reabsorbed, MAO inhibitors raise their concentrations in the synaptic cleft, which enhances neurotransmission.[7]

Types of depression [8]

Persistent depression

This illness usually results in a mood that lasts for two to three years. This kind of depression manifests in a variety of symptoms that might affect a patient's behavior for a long time.This illness usually results in a mood that lasts for two to three years. This kind of depression manifests in a variety of symptoms that might affect a patient's behavior for a long time.

Postnatal depression

After a baby is delivered, some mothers may suffer from a type of sadness called "Baby Blues." Mild anxiety and depression are common symptoms of this illness, which usually goes away two weeks after giving birth.

Bipolar depression

It encompasses euphoric or irritated states as well as profoundly low moods, which is why it is named It is known as maniac depression because it encompasses both euphoric or irritated states as well as profoundly depressed moods.

Seasonal effective disorder

People sometimes call this illness "winter depression." In the winter, when there is less sunshine, it usually shows up. Weight gain, more sleep, and a propensity to avoid social situations are common signs.

Medicinal herbs and phytochemicals used in depression

Depression is treated with a variety of traditional antidepressant types, including second-generation antidepressants, monoamine oxidase (MAO) inhibitors, and tricyclic antidepressants. MAO inhibitors work by blocking norepinephrine and the serotonin transporter (SERT), which raises synaptic levels and improves neurotransmission. As the main therapy, the monoamine inhibitors—tranylcypromine, phenelzine, isocarboxazid, and moclobemide—are typically recommended.[9] These inhibitors raise levels and improve transmission by blocking the norepinephrine and serotonin transporters (SERTs). These substances increase the activity of neurotransmissions.[10]

Medicinal herbs used in the treatment of depression

Throughout history, herbal remedies have been recognized as vital components of traditional treatment. Their ability to alleviate depression has garnered a lot of attention lately. Numerous research indicate that using herbal treatments can improve symptoms of depression. The effects of some medicinal plants have been compared to those of conventional antidepressants. These herbs help control serotonin, dopamine, and noradrenaline reuptake and have psychopharmacological effects on the nervous system similar to those of antidepressants. They also have an impact on the inhibition of monoamine oxidase (MAO) and the neuroendocrine system, which includes the hypothalamic-pituitary-adrenal (HPA) axis. The list of herbal remedies that may be used to treat depression is provided below.[14]

Green tea

The leaves of the Camellia sinensis plant are used to make green tea. Numerous beneficial qualities, including anti-inflammatory, anti-fibrotic, anti-cancer, and anti-neurodegenerative effects, have been shown. Polyphenols from Camellia sinensis, administered orally at 5, 10, and 20 mg/kg over seven days, improved depression-related behaviors and decreased blood cortisol levels, according to a new preclinical study. These results suggest that the hypothalamic-pituitary-adrenal (HPA) axis, which is known to have a role in the pathophysiology of depression, may be modulated by green tea polyphenols.[15]

An important bioactive substance, theanine is well-known for its remarkable anti-inflammatory and antioxidant properties. When combined with higher quantities of polyphenols and caffeine, it has demonstrated impressive outcomes. Other essential components of green tea include epicatechins, epigallocatechin gallate, and catechins.

St. John’s wort

According to recent studies, the therapeutic form of Hypericum perforatum, often known as St. John's wort, consists of a range of leaves and flowering tops that include compounds such xanthones, naphthodianthrones, flavonoids, phloroglucinols (especially hyperforin), and hypericin. Recent research indicates that H. perforatum can elevate mood similarly to traditional antidepressants such selective serotonin reuptake inhibitors and tricyclic antidepressants.[17]The short-term safety profile of St. John's Wort is shown to be better than that of traditional antidepressants by comparison. Hyperforin and hypericin, the herb's two main active ingredients, have been studied; the findings show that hyperforin is more effective than hypericin as an antidepressant. H. perforatum works in the brain's frontal lobe by blocking MAO-A and NAO-B, which reduces serotonin, dopamine, and norepinephrine synaptic reuptake. It also upregulates 5-HT2 receptors and downregulates beta receptors. This plant has been used to create and market

a number of pharmaceutical products in Iran, such as Perforan pills, Hypericaps, Hypericum STADA, and Hypericum 300.One of H. perforatum's primary functions is the overexpression of 5-HT receptors, which in turn causes the upregulation of neurons and, in the end, helps to decrease dopamine neurons' background activity. [19] Like SSRIs, this herb also affects the factor's overexpression at 5-HTAA receptors; it also prevents GABA3 from binding, which lowers the central nervous system's (CNS) storage capacity. By influencing N-methyl-D-aspartate receptors (NMDARs), H. perforatum performs essential functions similar to those of nootropics.[20]

Lavender

The blooming plant Lavender angustifolia, which is a member of the Lamiaceae family, is native to the Mediterranean area. This plant is well known for its ability to relieve intestinal pain, anxious stomach irritation, and a number of mental problems, such as restlessness and sleeplessness. Consequently, it contributes to strengthening the nervous system's resilience, which lessens depressive and exhausting sensation.Lavender blossoms are highly valued for their use in herbal tea and in the steam distillation of tinctures and essential oils. Long-term treatment to lavender oil dramatically decreased depression-like behaviors in rats, as evidenced by enhanced plus-maze and forced swimming tests (Hritcu et al., 2013). Four weeks of lavender aromatherapy improved the Edinburgh Postnatal Depression Scale scores of high-risk postpartum women in the research. Additionally, a group of 45 people who received imipramine and lavender oil as supplemental treatment for moderate depression had quicker and better results.[21]

Ashwagandha

Withania somnifera, commonly known as ashwagandha, is known to have adaptogenic properties. It has mostly been used to control the neuroendocrine axis of the hypothalamus, pituitary, and thyroid, which is linked to the onset of serious depression. Being classified as a "adaptogen," ashwagandha is known for its remarkable antioxidant qualities. Along with its ability to enhance memory, it is also known for its neuroprotective and anti-inflammatory properties. It is possible for Withania somnifera to cross the blood-brain barrier. W. somnifera may tolerate a wide range of stresses and help regulate psychological processes by interacting with GABA through receptor binding in several animal models, according to numerous clinical investigations.[28]

Saffron

Saffron, a perennial plant that is mostly produced in Iran and other countries like Greece and India, is a member of the Iridaceae family and is formally known as Crocus sativus L. The dried red stigmas of the Crocus sativus bloom, which retains a little amount of its yellow hue, are used to make the culinary spice known as saffron. Saffron has no harmful side effects when used to treat depression in traditional Persian medicine. According to studies, saffron effectively lowers mild to severe depression by preventing nerve cells from releasing serotonin. Patients who took 30 mg of saffron daily shown significant improvements in their depression scores on the Hamilton Rating Scale for Depression when compared to a placebo in two randomized controlled trials. A recent mini meta-analysis suggested that saffron supplementation could reduce symptoms in people experiencing depression.

Phytochemical against depression

Herbal phytochemicals are known to lower the risk of a number of dangerous illnesses, such as cardiovascular disease, neurological diseases, and autoimmune disorders. Notably, well-known polyphenols with strong anti-inflammatory and antioxidant properties include resveratrol, proanthocyanidin, quercetin, ferulic acid, and curcumin. These phytochemicals have continuously demonstrated neuroprotective qualities, suggesting that they may be able to lessen depressive symptoms. Table 1 lists these substances' antidepressant properties.

Carvacrol

Aromatic herbs such as thyme and oregano contain carvacrol, a phenolic monoterpene. Numerous beneficial properties, including anti-inflammatory, analgesic, antiarthritic, antiallergic, anticarcinogenic, antidiabetic, cardioprotective, gastroprotective, hepatoprotective, and neuroprotective activities, are demonstrated by this aromatic phytochemical [30]. One important component found in essential oils and aromatic plants is carvacrol. It has a major impact on depression and has demonstrated a variety of impacts on cognitive function. It has also been identified as a chemical flavonoid, while its safety assessment is still pending. The use of carvacrol has been the subject of several therapeutic investigations, particularly in women who experience depression at specific stages of the menstrual cycle. Its effects are linked to serotonin levels and the presence of metabolites in the nucleus accumbens and prefrontal cortex, highlighting its role in the serotonergic system.[31]

Curcumin

Curcuma longa, commonly referred to as turmeric, is the source of curcumin. It has antidepressant properties that monoamine oxidase A and B inhibit. It has been discovered that this plant chemical raises the brain's levels of neurotransmitters. Curcumin's antidepressant qualities support key theories of depression, particularly the monoamine and cytokine hypotheses. It has been shown that carvacrol treatment alters the brain's dopaminergic pathways, leading to increased dopamine and serotonin (5-HT) levels in the prefrontal cortex. [34, 35] When curcumin is taken orally, it has been shown to have low levels in tissues and plasma, as well as rapid metabolism and noticeable rapid excretion.The limited bioavailability of curcumin is likely due to its poor

solubility in water and inadequate absorption. Therefore, different approaches are being investigated to improve its bioavailability, such as employing absorption enhancers, structural analogs, liposomal formulations, and nanomaterials[36].

Ferulic acid

Plant cell walls, leaves, and seeds are the main natural sources of ferulic acid. Ferulic acid has been shown to have a number of neurotherapeutic advantages, including lowering glutamate excitotoxicity, affecting apoptosis, and raising reactive oxygen species (ROS) levels. The brain's increased indoleamine 2,3-dioxygenase activity causes an unusual shift in tryptophan metabolism, shifting it toward kynurenine instead of serotonin. Because ferulic acid has demonstrated promise as an antidepressant, this decrease in brain levels explains the effectiveness of some drugs, which should be enhanced.[39]

Proanthocynidin

Apples, cocoa, beans, grapes, and tea are among the plants that contain proanthocyanidin, a form of oligomeric and polymeric flavan-3-ol. Research has indicated that proanthocyanidin can decrease the overproduction of pro-inflammatory cytokines in the amygdala, prefrontal cortex, and hippocampal regions [44]. Xu et al. showed that giving mice oral proanthocyanidin at dosages of 25 and 50 mg/kg for seven days in a row reduces the amount of time they are immobile in tests involving forced swimming and tail suspension. Furthermore, proanthocyanidin therapy raised 5-HT levels in the frontal brain, hippocampus, and hypothalamus. The authors speculate that the central monoaminergic neurotransmitter pathways may be connected to proanthocyanidin's antidepressant effects.[45]

Resveratrol

Red wine and grapes are natural sources of resveratrol, a phenolic chemical. It is renowned for having remarkable neuroprotective properties. Resveratrol reduces the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which has a significant effect on antioxidant regulation. Additionally, it has been shown to have an antidepressant effect by influencing the metabolism of serotonin and noradrenaline. Resveratrol primarily modifies brain-derived neurotrophic factor (BDNF) levels to affect its effects. According to studies, resveratrol is an essential neuroprotective compound that may significantly boost neurogenesis and treat a variety of neurological disorders. Resveratrol also contains anti-aging properties and has demonstrated efficacy as a potent sleep aid. It is also related to monoaminergic systems and molecular indicators tied to depression, which are closely linked to both the hypothalamic-pituitary-thyroid axis and the HPA axis. [46,47]

Table 1: phytochemicals against depression.

Phytochemical	Dose	Study design	Effects and mechanisms
Carvacrol	12.5–50 mg/kg 12.5 mg/kg	Oral administration in mice Oral administration in rats	provide antidepressant effects that appear to rely on a connection with the brain's dopaminergiccircuits. Increase dopamine and 5-HT levels in the prefrontal cortex and hippocampal regions. Modify neurotransmitter levels to affect neuronal activity.
Curcumin	1.25–10 mg/kg 20–40 mg/kg	Oral administration in rats Intraperitoneal injection in mice	Shorten the forced swimming test's immobility period. Reverse bilateral olfactory bulbectomy-induced impairments in step-down passive avoidance and open-field hyperactivity. Enhance 5-HT level Restore biochemical and behavioral changes induced by the chronic stress Reverse the decreased immobility period and MAO activity induced chronic stress.
	10 mg/kg	Oral administration in mice	Reduce duration of immobility in forced swimming test May be associated with 5-HT_1A/1B and 5-HT_2C subtypes.
	10–20 mg/kg	Oral administration in rats	Attenuate the stress-induced hippocampus 5-HT_1A mRNA
Ferulic acid	100–250 mg/kg	Oral administration in mice	Attenuate stress-induced behavior Increase CREB phosphorylation and brain-derived neurotropic factor mRNA level in the hippocampus

L-Theanine	1–20 mg/kg	Oral administration in mice	Reduce immobility time in the forced swimming test and tail suspension test without ambulation in the open field test Antagonize reserpine-induced ptosis and hypothermia
Proanthocyanidin	25–50 mg/kg	Oral administration in mice	Reduce immobility period in the forced swimming test and tail suspension test Enhance 5-HT levels in hypothalamus, hypothalamus, and frontal cortex
Quercetin	20–40 mg/kg	Oral administration in mice	Prevent hyperactivation of the HPA axis
Resveratrol	20–80 mg/kg	Oral administration in mice	Decrease immobility period in the despair tests without influence on locomotor activity Enhance 5-HT and noradrenaline concentrations in the brain Reverse less weight gain, reduce sucrose preference and deficits in the shuttle box
	40–80 mg/kg	Oral administration in rats	Raise 5-HT, dopamine, and noradrenaline concentrations in brain Reduce MAO activity

Pharmacological properties

1. Monoamine Oxidase Inhibition (MAO Inhibition):

Certain herbs raise levels of neurotransmitters including serotonin, norepinephrine, and dopamine, which are frequently lacking in depression, by inhibiting the monoamine oxidase enzymes (MAO-A and MAO-B).

Example: Hypericin and hyperforin, found in Hypericum perforatum (St. John's Wort), inhibit MAO-A and MAO-B.

Effect: Enhances mood by increasing synaptic concentrations of monoamines.

2. Reuptake Inhibition of Neurotransmitters

Like traditional antidepressants (SSRIs, SNRIs), several natural substances block the reuptake of serotonin (5-HT), norepinephrine (NE), and dopamine (DA).

Example: Rhodiola rosea (rosavin, salidroside) and Withania somnifera (withanolides).

Effect: Improved synaptic transmission and mood stabilization.

3. Anti-inflammatory Activity

The pathophysiology of depression has been linked to chronic inflammation. Neuroinflammation can be decreased by natural substances that have anti-inflammatory properties.

Example: Curcuma longa (Curcumin), Panax ginseng, Bacopa monnieri.

Mechanism: Downregulation of pro-inflammatory cytokines (IL-6, TNF-α) and NF-κB pathway inhibition.

4. Antioxidant Activity

In depression, oxidative stress plays a role in neuronal damage. Antioxidants aid in protecting brain tissues and scavenging free radicals.

Example: Polyphenols from green tea (EGCG), resveratrol, quercetin, turmeric.

Effect: Reduced oxidative stress in the brain and improved neuroprotection.

5. HPA Axis Modulation

The hypothalamic-pituitary-adrenal (HPA) axis is often hyperactive in depressed individuals. Natural products can help normalize cortisol levels and reduce stress response.

Example: Ashwagandha, Rhodiola, Licorice.

Effect: Modulate glucocorticoid receptors and reduce stress-induced neurochemical changes.

6. Neurotrophic Activity

Some phytochemicals promote neurogenesis and increase levels of brain-derived neurotrophic factor (BDNF), which is critical for mood regulation.

Example: Ginkgo biloba, Curcuma longa, Bacopa monnieri.

Mechanism: Activation of CREB-BDNF pathway, enhancing synaptic plasticity.

7. GABAergic and Glutamatergic Modulation

Certain herbal agents interact with GABA and glutamate systems, influencing anxiety and mood.

Example: Valeriana officinalis, Passiflora incarnata.

Effect: GABA agonism and NMDA receptor antagonism for calming effects.

8. Serotonergic Activity

Some herbs act on serotonin receptors or stimulate serotonin production.

Example: Griffonia simplicifolia (5-HTP precursor), St. John’s Wort.

Effect: Enhances serotonergic tone, reducing depressive symptoms.

Conclusion

Throughout history, the understanding of herbs has demonstrated significant benefits for humanity. This system was traditionally based on the fundamental principle of treating ailments with the resources readily available in our environment. In recent years, advancements have emerged that allow for the exploration of phytochemicals derived from various sources. The aforementioned herbs and phytochemicals are associated with different hypotheses and mechanisms related to depression. For instance, green tea contains the phytochemical L-theanine, which is known to enhance the levels of neurotransmitters and inhibit neuronal apoptosis.

Preclinical and clinical studies have shown how these medications work in the brain to reduce depression and its symptoms. Phytomedicinal herbs are preferred due to their minimal side effects compared to traditional antidepressants, and they may also be more affordable for many. With a favorable safety profile, these herbs have shown promising results in preclinical trials, though clinical studies are still scarce. It's crucial to validate the effectiveness of phytomedicine through clinical research and to fully understand their mechanisms of action.

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