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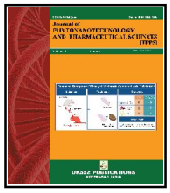

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Medicinal plants in the management of depression: A comprehensive review

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Abstract

Depression represents a major global health challenge characterized by persistent sadness, anhedonia, and impaired functioning. This review examines the pathogenesis of depression involving neurotransmitter imbalances, HPA axis dysregulation, neuroinflammation, and impaired neuroplasticity, alongside its substantial disease burden. While conventional antidepressants provide symptomatic relief, their limitations including side effects and delayed onset have spurred interest in phytotherapeutic alternatives. This paper evaluates 16 medicinal plants, *i.e.*, St. John's Wort, Saffron, Rhodiola rosea, Ashwagandha, *Bacopa monnieri*, Curcumin, Lavender, *Ginkgo biloba*, Kava, Valerian, Lemon balm, Passion flower, *Centella asiatica*, *Mucuna pruriens*, *Schisandra chinensis*, and Holy basil for their antidepressant mechanisms and clinical evidence. These herbs demonstrate multi-targeted actions through monoamine modulation, GABAergic enhancement, BDNF upregulation, HPA axis regulation, antioxidant effects, and anti-inflammatory properties. Clinical trials indicate efficacy comparable to conventional antidepressants for mild-to-moderate depression, often with superior tolerability. However, challenges remain regarding standardization, drug interactions, bioavailability, and long-term safety. Phytotherapy offers promising adjunctive and alternative strategies for depression management, particularly for patients experiencing treatment resistance, side effect burden, or preference for natural remedies.

1. Introduction

Depression is a common and serious mental disorder characterized by persistent feelings of sadness, hopelessness, and a loss of interest or pleasure in activities that were once enjoyable. It significantly affects how an individual feels, thinks, and manages daily activities (McCarter, 2008). Clinically, depression presents with a wide range of emotional and physical symptoms, including persistent low mood, fatigue or lack of energy, anhedonia, changes in appetite or body weight, sleep disturbances (insomnia or hypersomnia), impaired concentration, feelings of guilt or worthlessness, and recurrent thoughts of death or suicide. Depressive disorders encompass several subtypes. Major depressive disorder (MDD) is characterized by episodes of severe depressive symptoms that interfere with daily functioning (Tolentino and Schmidt, 2018). Persistent depressive disorder (dysthymia) is a chronic form of depression lasting for at least two years. Bipolar depression occurs during the depressive phase of bipolar disorder, while seasonal affective disorder (SAD) is associated with seasonal changes, particularly during winter months. Postpartum depression affects women following childbirth and can have profound consequences for both mother and child. Depression represents a major global public health challenge (Parker *et al.,* 2018). According to the World Health Organization, more than 280 million people worldwide suffer from depression, making it the leading cause of disability globally and a major contributor to the overall burden of disease. Depression is more prevalent in women than in men, with peak onset typically occurring between 18 and 29 years of age. However, it affects individuals across all age groups, including children, adolescents, adults, and the elderly. A higher prevalence has been reported in low and middle-income countries, largely due to socioeconomic stressors, limited access to mental health care, stigma, and lack of awareness, which often result in underdiagnosis and undertreatment (Zhang *et al.,* 2025).

1.1 Pathogenesis

Depression is a multifactorial disorder arising from a complex interaction of biological, psychological, and environmental factors. One of the central mechanisms involves neurotransmitter imbalance, particularly reduced levels of serotonin, norepinephrine, and dopamine, which play a crucial role in mood regulation. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is another key contributor. Chronic stress leads to sustained activation of the HPA axis, resulting in elevated cortisol levels that negatively impact mood regulation, neurogenesis, and cognitive function.Impaired neuroplasticity and reduced neurogenesis also play a significant role in the pathophysiology of depression. Decreased expression of brain-derived neurotrophic factor (BDNF), especially in the Hippocampus, has been associated with neuronal atrophy and emotional and cognitive dysfunction. Genetic factors further contribute to disease susceptibility, with several genes involved in neurotransmission and stress response being implicated (Hasler, 2010).

In addition, increasing evidence supports the role of inflammation and immune dysregulation in depression. Elevated levels of pro-

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inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been consistently observed in individuals with depressive disorders (Raison *et al.,* 2006). Circadian rhythm disturbances, including altered sleep-wake cycles and melatonin secretion, further contribute to mood instability. More recently, the gut-brain axis has gained attention, with studies demonstrating that alterations in gut microbiota composition may influence neuroinflammation, neurotransmitter production, and depressive symptoms (Cui *et al.,* 2024).

1.1.1 Risk factors

Several risk factors increase the likelihood of developing depression. These include biological factors such as genetic predisposition and neurotransmitter dysregulation; psychological factors such as low self-esteem, early-life trauma, and chronic stress; and social factors including poverty, unemployment, social isolation, and family conflict (Shadrina *et al.,* 2018). Furthermore, chronic medical conditions such as diabetes, cardiovascular diseases, and cancer are strongly associated with an increased risk of depression (Aan *et al.,* 2009).

1.1.2 Burden of disease

Depression is associated with substantial morbidity and mortality. It significantly reduces quality of life, impairs occupational and social functioning, and increases healthcare utilization and economic costs. Notably, depression is a major risk factor for suicide, with nearly 800,000 deaths reported globally each year. It frequently coexists with other psychiatric disorders such as anxiety and is commonly associated with chronic physical illnesses, further compounding its overall burden (Zhang *et al.,* 2025).

1.2 Management

The management of depression includes both pharmacological and non-pharmacological approaches. Pharmacological treatment primarily involves antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) (Cuijpers *et al.,* 2021). Non-pharmacological interventions include psychotherapeutic approaches such as cognitive behavioral therapy (CBT), interpersonal therapy (IPT), and mindfulness-based therapies. Lifestyle modifications, including regular physical activity, a balanced diet, and adequate sleep, are also beneficial. In severe or treatment-resistant cases, electroconvulsive therapy (ECT) and hospitalization may be required (Karrouri *et al.,* 2021). Despite the effectiveness of conventional antidepressant therapies, their use is often limited by adverse effects, delayed onset of action, and poor patient compliance. These limitations have driven growing interest in alternative therapeutic strategies. Natural sources, particularly plant-derived bioactive compounds, have shown promising antidepressant potential with fewer adverse effects. Therefore, the current review focuses on the role of medicinal plants and phytoconstituents in the management of depression.

2. Plant-based therapeutic approaches in the management of depression

Plant-based therapies have gained attention as alternative or adjunctive treatments for depression due to the limitations of conventional antidepressants, including delayed onset of action, side effects, and variable patient response. These therapies exert antidepressant effects through multiple mechanisms, such as modulation of neurotransmitter systems, regulation of the hypothalamic-pituitary-adrenal axis, reduction of neuroinflammation and oxidative stress, enhancement of neuroplasticity, and influence on the gut-brain axis. Bioactive compounds derived from plants, including flavonoids, alkaloids, terpenoids, and polyphenols, have shown promising efficacy in preclinical and clinical studies. This review discusses the antidepressant potential, underlying mechanisms, and scientific evidence supporting plant-based interventions in depression.

2.1 St. John's Wort (*Hypericum perforatum* L.)

St. John's Wort is a flowering plant widely used in the treatment of mild to moderate depression. It contains several active compounds, including hypericin and hyperforin, which are believed to exert antidepressant effects by inhibiting the reuptake of neurotransmitters such as serotonin, dopamine, and norepinephrine mechanisms similar to conventional antidepressants Clinical studies and meta-analyses have shown that standardized extracts of St. John's Wort are more effective than placebo and equally effective as standard antidepressants like SSRIs (*e.g.,* fluoxetine) in treating mild to moderate depression, with fewer side effects. However, St. John's Wort can interact with many medications, including antidepressants, birth control pills, warfarin, and antiretrovirals, due to its strong induction of the cytochrome P450 enzymes (especially CYP3A4). Therefore, although it is effective, its use must be cautious, especially when taken along with other medications (Canenguez *et al.,* 2022).

2.2 Saffron (*Crocus sativus* L.)

Saffron, derived from the dried stigmas of the *Crocus sativus* L. flower, is a traditional spice known not only for its culinary value but also for its therapeutic potential in mental health, especially in depression. The major active constituents of saffron include crocin, crocetin, safranal, and picrocrocin. These compounds are believed to exert antidepressant effects through several mechanisms, such as: Inhibiting the reuptake of serotonin, dopamine, and norepinephrine, thereby increasing their levels in the brain (Hausenblas *et al.,* 2013). Antioxidant and anti-inflammatory activity, which may reduce neuroinflammation often associated with depression. Several randomized clinical trials have shown that saffron extract (usually 30 mg/day) is as effective as conventional antidepressants like fluoxetine or imipramine in mild to moderate depression, with fewer side effects. Saffron is generally well-tolerated, but high doses may cause toxicity, including nausea, vomiting, dizziness, or in rare cases, uterine stimulation (Omidkhoda *et al.,* 2022).

2.3 Arctic root (*Rhodiola rosea* L.)

It is an adaptogenic herb traditionally used in Russian and Scandinavian medicine to combat stress, fatigue, and low mood. In recent years, it has gained attention for its antidepressant and anxiolytic effects. The primary active compounds in *Rhodiola* include rosavin, salidroside, and tyrosol, which contribute to its stress-protective and mood-enhancing properties. *Rhodiola* is believed to regulate the hypothalamic-pituitary-adrenal (HPA) axis, thereby reducing stress hormone (cortisol) levels. It enhances the sensitivity of serotonin and dopamine receptors in the brain, which helps improve mood and cognitive function. It also shows antioxidant and neuroprotective effects, which may contribute to its antidepressant activity. Clinical trials suggest *R. rosea* extract can reduce symptoms

of mild to moderate depression, improve energy levels, and enhance mental performance, particularly under stress. It has a favorable safety profile, with fewer side effects compared to standard antidepressants (Mao *et al,* 2015).

2.4 Ashwagandha (*Withania somnifera* (L.) Dunal)

Ashwagandha, also known as Indian ginseng or winter cherry, is a key herb in Ayurvedic medicine, traditionally used as a Rasayana (rejuvenator) to promote mental health, vitality, and resilience to stress. The major active constituents include withanolides, withaferin A, and alkaloids, which possess adaptogenic, anti-inflammatory, and neuroprotective properties. Ashwagandha helps regulate the hypothalamic-pituitary-adrenal (HPA) axis, thereby reducing cortisol levels, which are often elevated in stress-related depression (Wiciński *et al.,* 2023). It modulates GABAergic and serotonergic neurotransmission, contributing to its anxiolytic and antidepressant effects. It protects neurons from oxidative stress and improves brain-derived neurotrophic factor (BDNF) levels, which are typically reduced in depression. A double-blind, placebo-controlled study found that Ashwagandha extract significantly reduced stress and depressive symptoms in adults with chronic stress, with excellent safety and tolerability. It has also shown benefit in comorbid anxiety and depression when used as an adjunct to standard therapy (Lopresti *et al.,* 2019).

2.5 Brahmi (*Bacopa monnieri* (L.) Pennell)

It is a traditional Ayurvedic herb renowned for its nootropic (cognitive-enhancing), adaptogenic, and neuroprotective effects. It is increasingly being studied for its antidepressant properties, especially in cases where depression coexists with cognitive impairment, stress, or anxiety. The primary active compounds in *Bacopa* include bacosides A and B, which enhance synaptic activity, act as antioxidants, and support neural regeneration. *Bacopa* increases serotonin levels in the Hippocampus and may modulate dopaminergic and cholinergic systems, contributing to its mood-elevating effects (Oommen *et al.,* 2016) It reduces oxidative stress and lipid peroxidation in the brain, which is often elevated in depression. *Bacopa* also supports neuroplasticity and enhances memory and learning, which are often impaired in depressive disorders. A randomized, double-blind, placebo-controlled trial showed that *Bacopa* extract improved mood, reduced anxiety and depression scores, and enhanced cognitive performance in elderly participants. It has shown potential in reducing stress-induced behavioral changes and enhancing mental well-being in both clinical and preclinical studies. Modern research has recognized *Bacopa* for its antidepressant, anxiolytic, and neuroprotective properties, making it a promising candidate for the treatment of mood disorders, including depression. The key phytochemicals in *Bacopa*, namely bacosides A and B, have been shown to exert multiple neuropharmacological effects. These compounds not only stimulate serotonin, dopamine, and GABAergic neurotransmission, but also improve neuronal communication, which is vital for maintaining emotional balance (Sairam *et al.,* 2002). *Bacopa* also exhibits potent antioxidant activity, scavenging free radicals and reducing lipid peroxidation, thus protecting neurons from oxidative stress, a contributing factor in depression. Experimental studies in rodents have demonstrated that *Bacopa* extract can reverse depression-like behaviors in forced swim and tail suspension tests, which are standard models for antidepressant screening. In addition, *Bacopa* has been shown to upregulate brain-derived neurotrophic factor (BDNF), a protein that supports neuron survival and plasticity, both of which are often compromised in depressive disorders. Clinically, *Bacopa* has been evaluated in elderly populations where it not only reduced depression and anxiety scores, but also enhanced working memory, attention, and learning capacity. The herb is considered safe for long-term use, with minimal side effects, mainly gastrointestinal discomfort at high doses. *Bacopa's* adaptogenic effects also contribute to its antidepressant action by modulating the hypothalamic-pituitary-adrenal (HPA) axis, thereby normalizing cortisol levels in stress-induced depression. Unlike conventional antidepressants, *Bacopa* offers a dual benefit: it not only improves emotional well-being, but also enhances cognitive performance, making it ideal for populations such as students, elderly individuals, and those with stress-related mental fatigue. These findings support the use of *B. monnieri* as a natural, multifunctional remedy for depression and related disorders (Brimson *et al.,* 2021).

2.6 Curcumin (*Curcuma longa* L.)

Curcumin, the principal bioactive compound of turmeric (*Curcuma longa* L.), has gained significant attention in recent years for its antidepressant, anti-inflammatory, and neuroprotective effects. Traditionally used in Ayurvedic and Chinese medicine, curcumin is now being scientifically validated as a promising adjunct or alternative treatment for major depressive disorder (MDD) and stress-related mood disturbances. Curcumin acts through multiple mechanisms. It modulates neurotransmitter levels, including serotonin, dopamine, and norepinephrine, much like conventional antidepressants. It also enhances brain-derived neurotrophic factor (BDNF) expression, a protein essential for neuroplasticity and neural regeneration, which is often found to be decreased in depression. Furthermore, curcumin reduces the activity of pro-inflammatory cytokines (such as IL-6 and TNF-α) and inhibits the NF-κB pathway, helping to counteract neuroinflammation, which is now recognized as a contributor to the pathophysiology of depression. Several clinical trials have demonstrated the efficacy of curcumin in alleviating depressive symptoms (Matias *et al.,* 2021). A notable double-blind, randomized controlled trial found that curcumin (500-1000 mg/day) significantly improved symptoms in patients with major depressive disorder, and its effects were comparable to those of fluoxetine, a commonly used antidepressant. Additionally, curcumin is considered safe and well-tolerated, with very few side effects when taken at appropriate doses. However, curcumin has poor oral bioavailability, meaning it is not easily absorbed in the body. This limitation is often addressed by combining it with piperine (from black pepper), which enhances curcumin's absorption by up to 2000%. Formulations like curcumin phytosomes, nanoparticles, and liposomes are also being developed to improve its clinical utility. Given its ability to target oxidative stress, inflammation, and neurotransmitter imbalance, curcumin represents a multitargeted, natural approach to depression management, especially in patients who also suffer from inflammatory or metabolic disorders (Ramaholimihaso *et al.,* 2020).

2.7 Lavender (*Lavandula angustifolia* Mill.)

It is a fragrant herb traditionally used for its calming and soothing properties, has gained recognition in modern pharmacology for its antidepressant and anxiolytic effects. Both aromatherapy and oral lavender extracts have been evaluated in clinical studies for their mood-enhancing potential, particularly in individuals with mild to moderate depression, anxiety, and stress-related disorders. The active

components in lavender include linalool and linalyl acetate, which are believed to act on the central nervous system by modulating GABAergic neurotransmission, similar to the action of benzodiazepines (Nikfargam *et al.,* 2013). These compounds exert calming and sedative effects without causing dependence or cognitive impairment, which is a common issue with synthetic anxiolytics. Lavender enhances GABA-A receptor activity, leading to reduced neuronal excitability, and produces a calming effect. It also modulates serotonin and dopamine levels, contributing to mood elevation. Lavender reduces cortisol (stress hormone) levels, thus supporting the hypothalamic-pituitary-adrenal (HPA) axis balance, a key factor in depression. A patented oral lavender oil preparation called Silexan has shown significant improvement in symptoms of depression and anxiety in several randomized controlled trials. One clinical study found Silexan to be as effective as paroxetine (an SSRI) in patients with generalized anxiety disorder and comorbid depression, but with fewer side effects and better tolerance. Inhalation of lavender essential oil has also demonstrated short-term reductions in depressive symptoms, especially in postpartum women, elderly individuals, and those undergoing stressful situations like surgery or exams. Lavender is generally well-tolerated, though mild side effects such as nausea or allergic reactions may occur in sensitive individuals. It is non-sedative at therapeutic doses and does not impair cognitive or psychomotor function, making it a valuable adjunct or alternative in mood disorders (Firoozeei *et al.,* 2021).

2.8 Ginkgo (*Ginkgo biloba* L.)

It is an ancient tree species, and has gained recognition as a potential adjunctive therapy for depression, particularly in elderly patients and individuals with cognitive decline. Its primary active constituents include flavonoids (quercetin, kaempferol, isorhamnetin) and terpenoids (ginkgolides A, B, C, J, and bilobalide), which contribute to its diverse neuropharmacological effects (Dai *et al.,* 2018). The antidepressant potential of *Ginkgo biloba* L. is attributed to multiple mechanisms. It exhibits strong antioxidant activity, neutralizing free radicals and protecting neurons from oxidative stress, a known contributor to depression pathogenesis. *Ginkgo* also modulates the levels and activity of key neurotransmitters such as serotonin, dopamine, and norepinephrine by influencing receptor sensitivity and uptake, thereby improving mood regulation (Lin *et al.,* 2024). Additionally, it enhances cerebral blood flow through vasodilatory effects mediated by ginkgolides, improving oxygenation and nutrient supply to mood-regulating brain regions like the prefrontal cortex and hippocampus. The extract bilobalide has been shown to exert anti-inflammatory and neuroprotective effects by reducing pro-inflammatory cytokines (IL-6, TNF-α), preserving mitochondrial function, and supporting neuroplasticity. Preclinical studies also indicate that *Ginkgo* upregulates brain-derived neurotrophic factor (BDNF), which is essential for neuronal growth and synaptic plasticity, and is often found reduced in depressed individuals. Clinical trials support the efficacy of *G. biloba* in alleviating depressive symptoms. A randomized, placebo-controlled trial using standardized extract EGb 761 demonstrated significant improvement in depressive symptoms among elderly patients with major depression and coexisting cognitive impairment. Furthermore, *G. biloba,* when used in combination with conventional antidepressants such as selective serotonin reuptake inhibitors (SSRIs), enhanced treatment efficacy and tolerability, especially in late-life depression. A meta-analysis also found modest but significant benefits of *G. biloba* in reducing depressive symptoms, particularly in populations with neuro degenerative conditions. These findings, combined with its favorable safety profile and cognitive-enhancing properties, make *G. biloba* a promising natural option for integrative management of depression, especially when oxidative stress and vascular dysfunction are involved (Wang *et al.,* 2020).

2.9 Kava (*Piper methysticum* G. Forst.)

It is a plant native to the South Pacific, is traditionally consumed as a ceremonial and therapeutic beverage for its calming and mood-enhancing effects. In recent decades, Kava has drawn scientific interest for its role in alleviating symptoms of depression, particularly when co-occurring with anxiety disorders. The pharmacologically active compounds in Kava are known as kavalactones, of which the major ones include kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin. These kavalactones exert their effects primarily through modulation of the GABAergic system, enhancing GABA-A receptor activity, which contributes to the anxiolytic and mood-stabilizing properties of Kava without the sedative effects commonly associated with benzodiazepines. Additionally, Kava influences dopaminergic transmission and inhibits norepinephrine reuptake, thereby improving motivation and alleviating anhedonia key features of depression. Kavalactones also show monoamine oxidase B (MAO-B) inhibition, which may increase the availability of dopamine in the central nervous system. Clinical studies support the efficacy of Kava in treating mood disorders, especially those with an anxiety-depression overlap (Soares *et al*., 2022). A randomized controlled trial demonstrated that standardized Kava extract significantly reduced depression scores on the hamilton depression rating scale (HAM-D) in patients with generalized anxiety disorder (GAD), suggesting antidepressant effects secondary to its anxiolytic action. Moreover, patients who had mild to moderate depression with comorbid anxiety showed significant symptom reduction with Kava extract treatment over six weeks, with minimal adverse effects and good tolerability. The adaptogenic and calming effects of Kava help regulate the hypothalamic-pituitary-adrenal (HPA) axis, which is often dysregulated in stress-related depression. Despite these promising results, concerns have been raised over hepatotoxicity associated with long-term or unsupervised use of certain Kava extracts, particularly those made from leaves or stems rather than the traditional root-only preparations. When used correctly, *i.e.,* aqueous extracts from peeled roots it remains a well-tolerated and effective herbal option for managing depression, especially when anxiety is a predominant feature (Sarris *et al*., 2009).

2.10 Valerian root (*Valeriana officinalis* L.)

It is a perennial herb widely recognized for its sedative, anxiolytic, and sleep-promoting properties. While it is most commonly used for insomnia and anxiety, emerging evidence suggests its potential role as an adjunctive therapy for depression, especially when associated with sleep disturbances and restlessness. The main bioactive constituents of Valerian root include valerenic acid, valepotriates (valtrate and isovaltrate), bornyl acetate, and volatile oils such as linalool and caryophyllene. (Murphy *et al*., 2010). These compounds exert central nervous system effects primarily through modulation of GABAergic neurotransmission specifically by inhibiting GABA breakdown and enhancing GABA-A receptor binding, thus promoting relaxation and mood stabilization. Valerenic acid, in particular, is known to bind to β-subunits of the GABA-A receptor,

exerting anxiolytic and mild antidepressant-like effects. In addition, Valerian exhibits mild serotonergic and dopaminergic modulation, which may further contribute to mood elevation. Although, clinical trials on Valerian's antidepressant efficacy are limited compared to its anxiolytic studies, some human and animal studies suggest beneficial effects. In a double-blind, randomized controlled trial, patients with comorbid insomnia and mild depressive symptoms experienced significant improvement in sleep quality and a reduction in depression scores following treatment with Valerian extract. Preclinical research has also demonstrated antidepressant-like effects in rodent models, including the forced swim test and tail suspension test, where Valerian root extract reduced immobility time, a measure of behavioral despair. (Cases *et al*., 2011). These effects may stem from a combination of neurotransmitter regulation, sleep restoration, and stress reduction, especially in individuals with depression driven by insomnia or chronic stress. Valerian is generally considered safe and well-tolerated, though some individuals may experience mild side effects such as dizziness or gastrointestinal discomfort. Its non-habit-forming nature makes it a valuable herbal option for integrative depression management, particularly when sleep disturbances or anxiety are coexisting symptoms (Benke *et al*., 2009).

2.11 Lemon balm (*Melissa officinalis* L.)

It is a fragrant, lemon-scented herb from the mint family traditionally used to relieve stress, promote relaxation, and improve mood. Its growing popularity in phytotherapy for mood disorders stems from its anxiolytic, sedative, and mild antidepressant properties, particularly in individuals with stress-induced or anxiety-associated depression. (Cases *et al*., 2011). The primary active compounds in Lemon balm include rosmarinic acid, caffeic acid, flavonoids (such as luteolin and apigenin), and terpenes like citronellal, geranial, and nerol. These constituents contribute to Lemon balm's multi-targeted neuropharmacological activity (Ghazizadeh *et al*., 2021). One key mechanism is the inhibition of GABA transaminase, leading to increased GABA levels in the brain, which exerts calming and mood-enhancing effects. Additionally, rosmarinic acid has been shown to exert monoamine oxidase (MAO-A) inhibitory effects, potentially enhancing serotonin and dopamine availability, which are critical in the pathophysiology of depression. Lemon balm also exhibits antioxidant and anti-inflammatory properties, helping to reduce neuroinflammation, a contributor to mood dysregulation. Clinical and experimental studies support the antidepressant potential of Lemon balm. A randomized, double-blind, placebo-controlled trial reported that a standardized Lemon balm extract significantly improved self-reported mood, calmness, and alertness in healthy volunteers, and reduced agitation and depression symptoms in patients with mild to moderate mood disorders. In another clinical study, Lemon balm combined with other calming herbs such as Valerian was found to reduce symptoms of depression and anxiety in menopausal women. In animal models, Lemon balm extracts reduced immobility time in forced swim and tail suspension tests, indicating antidepressant-like activity, potentially through modulation of the HPA axis and monoaminergic systems. The herb is generally well-tolerated, non-sedating at therapeutic doses, and does not impair cognitive or psychomotor functions, making it an attractive option for those seeking a gentle, natural adjunct in the management of depression, especially when linked with stress and sleep disorders (Scholey *et al*., 2014).

2.12 Passion flower (*Passiflora incarnata* L.)

It is a climbing vine native to the Americas, traditionally used in herbal medicine for treating insomnia, anxiety, and nervous disorders. In recent years, it has gained scientific attention for its antidepressant and anxiolytic effects, especially in cases of depression associated with agitation, stress, or sleep disturbances. The key active constituents of Passion flower include flavonoids (*e.g.,* vitexin, isovitexin, orientin, chrysin), alkaloids (harmane, harmine), and glycosides, which together contribute to its neuropharmacological effects. The primary mechanism of action involves enhancement of GABAergic transmission. Flavonoids in Passion flower are known to bind to GABA-A receptors, mimicking GABA's inhibitory effect and producing a calming influence on the central nervous system. This GABAergic activity reduces neuronal hyperexcitability, thereby easing symptoms of anxiety and indirectly improving depressive mood states. (Elsas *et al*., 2010). Passion flower may also exert modest monoaminergic activity, influencing levels of serotonin and dopamine, which are crucial in mood regulation. Clinical and preclinical studies support the antidepressant efficacy of Passion flower. A randomized controlled trial found Passion flower extract to be as effective as oxazepam, a benzodiazepine, in treating generalized anxiety disorder, with fewer side effects such as sedation or impairment of work performance. Although, this study focused on anxiety, secondary improvements in mood and sleep were also noted, indicating benefit for individuals with mixed anxiety-depressive states. Animal studies have demonstrated that Passion flower extract reduces immobility time in forced swim and tail suspension tests, standard models for evaluating antidepressant activity. These effects are believed to result from both GABAergic modulation and antioxidant activity, as Passion flower flavonoids reduce oxidative stress markers in brain tissue, a known contributor to depressive pathophysiology. Passion flower is generally well-tolerated and non-habit-forming, with rare side effects such as dizziness or gastrointestinal discomfort. Its dual benefit on mood and sleep quality makes it a valuable natural adjunct in the management of mild to moderate depression, particularly when anxiety or insomnia is a significant component (Akhondzadeh *et al*., 2001).

2.13 Indian pennywort (*Centella asiatica* (L.) Urban)

It is commonly known as Gotu kola, is a small, herbaceous plant widely used in Ayurvedic and Traditional Chinese Medicine for promoting mental clarity, cognitive health, and emotional balance. In recent years, it has attracted interest as a natural remedy for depression, particularly due to its nootropic, adaptogenic, and neuroprotective properties. The major bioactive constituents of *C. asiatica* include triterpenoid saponins such as asiaticoside, madecassoside, asiatic acid, and madecassic acid, which play key roles in modulating central nervous system function. These compounds contribute to enhanced neuronal communication, antioxidant defense, and anti-inflammatory activity, all of which are crucial in managing depressive disorders. One key mechanism involves the upregulation of brain-derived neurotrophic factor (BDNF) and neurogenesis in the Hippocampus, thereby improving synaptic plasticity and mood regulation. Additionally, *C. asiatica* modulates serotonin and dopamine neurotransmission, which helps alleviate low mood and emotional instability (Rana and Galani, 2014). The plant also acts on the HPA axis, reducing cortisol levels and improving resilience to chronic stress, one of the major triggers for depression.

Clinical and experimental studies support the antidepressant potential of *C. asiatica*. A double-blind, placebo-controlled study demonstrated that daily supplementation with Gotu kola extract for 60 days significantly reduced symptoms of anxiety, stress, and depression in healthy elderly participants, along with improvement in cognitive function. In animal models, *C. asiatica* extract reduced immobility in forced swim and tail suspension tests behavioral markers of antidepressant activity likely mediated through its serotonergic effects and BDNF expression. In addition, *Centella* has been shown to improve sleep quality, reduce oxidative stress, and protect hippocampal neurons, which are often compromised in individuals with chronic depression. The herb is well-tolerated and considered safe for long-term use, with minimal side effects primarily limited to mild gastrointestinal discomfort. Its broad-spectrum neuropharmacological profile and ability to enhance both mood and cognition make *C. asiatica* a promising herbal option in the integrative treatment of depression, especially in cases involving stress, fatigue, and cognitive decline (Mando *et al.,* 2024).

2.14 Monkey tamarind (*Mucuna pruriens* (L.) DC.)

It is commonly known as velvet bean, is a tropical legume traditionally used in Ayurvedic medicine for enhancing vitality, neurological function, and mood. In recent years, it has emerged as a promising natural antidepressant, primarily due to its high content of L-3,4-dihydroxyphenylalanine (L-DOPA) a direct precursor to dopamine, a neurotransmitter significantly involved in mood regulation, motivation, and reward processing. In addition to L-DOPA, *Mucuna* contains other bioactive compounds including mucunine, mucunadine, â-sitosterol, gallic acid, and tryptamines, all of which contribute to its neuromodulatory and adaptogenic properties. The central mechanism of its antidepressant effect lies in boosting central dopaminergic activity, particularly in the mesolimbic system, where dopamine deficiency is strongly linked to anhedonia and depression. Moreover, *Mucuna* exhibits antioxidant, anti-inflammatory, and neuroprotective effects, reducing oxidative stress and preserving neuronal function, which are critical in chronic stress-related depression. (Mata *et al*., 2024). Clinical and experimental data support the efficacy of *Mucuna pruriens* in mood disorders. A randomized controlled trial in Parkinson's disease patients who often experience depression due to dopamine deficiency found that *Mucuna* seed powder improved mood and reduced depressive symptoms, alongside motor benefits, due to its natural L-DOPA content. In healthy individuals, *Mucuna* supplementation has been associated with improved mood, increased motivation, and reduced stress-related symptoms, likely due to enhanced dopamine synthesis and stress resilience. Animal studies also corroborate these findings; administration of *Mucuna* extract in rodents reduced immobility in the forced swim test and tail suspension test, indicating significant antidepressant-like activity. Furthermore, *Mucuna* has shown potential to normalize cortisol levels, suggesting regulation of the HPA axis, a key system implicated in the pathophysiology of depression. It is generally safe and well-tolerated, although caution is advised in individuals with cardiovascular conditions or those using MAO inhibitors, due to its dopaminergic effects. Given its dual role as a mood enhancer and neurorestorative agent, *M. pruriens* presents a compelling herbal option for treating dopamine-deficiency-related depression, particularly in stress-induced or neurodegenerative contexts. (Hammoud *et al*., 2025).

2.15 Magnolia berry (*Schisandra chinensis* (Turcz.) Baill.)

It is commonly known as magnolia vine or five-flavor berry, is a traditional adaptogenic herb used in Chinese, Korean, and Russian medicine to combat fatigue, enhance vitality, and support emotional well-being. In recent years, it has gained attention for its antidepressant and anti-stress effects, especially in individuals experiencing fatigue-related or stress-induced depression. The primary bioactive constituents include lignans such as schisandrin, schisandrin A, B, and C, gomisin A, and deoxyschisandrin, which exert neuroprotective, anti-inflammatory, and adaptogenic effects. These compounds enhance mitochondrial function, reduce reactive oxygen species, and modulate hypothalamic-pituitary-adrenal (HPA) axis activity key mechanisms in preventing the neurochemical and behavioral changes seen in depression. *Schisandra* also influences monoaminergic systems, including the dopaminergic and serotonergic pathways, which helps correct neurotransmitter imbalances associated with low mood and cognitive dysfunction. Experimental studies strongly support the antidepressant properties of *Schisandra chinensis*. In rodent models of depression such as the chronic mild stress and forced swim test, *Schisandra* extract significantly reduced depressive behaviors, increased locomotor activity, and elevated brain levels of serotonin and dopamine. These findings were accompanied by upregulation of brain-derived neurotrophic factor (BDNF) in the Hippocampus, suggesting enhanced neuroplasticity and resilience against stress-induced neuronal damage. One study showed that schisandrin B not only improved behavior in depressed rats but also reduced corticosterone levels and normalized Hippocampal neurogenesis, key markers of HPA axis stabilization. While high-quality clinical trials are limited, *Schisandra* has been used in combination with other herbs in traditional formulas for neurasthenia, mental exhaustion, and anxiety-depression syndromes, with reports of improved mood, cognition, and sleep. It is generally considered safe and well-tolerated, with minimal side effects when used within therapeutic ranges. Its multi-targeted action on stress response, neurotransmission, and neurotrophic factors makes *Schisandra chinensis* a valuable herbal candidate for managing mild to moderate depression, particularly when accompanied by fatigue, cognitive impairment, or stress overload (Yan and Wan, 2016).

2.16 Holy basil (*Ocimum tenuiflorum* L.)

It is also known as Tulsi, is a revered adaptogenic herb in Ayurvedic medicine, traditionally used to promote spiritual clarity, reduce stress, and enhance overall mental and physical resilience. Increasing scientific evidence supports its use in the management of depression, particularly when stress, anxiety, or fatigue are contributing factors. Tulsi is rich in bioactive phytochemicals, including eugenol, ursolic acid, rosmarinic acid, linalool, apigenin, and ocimarin, which exhibit anti-inflammatory, antioxidant, neuroprotective, and anxiolytic properties (Cohen, 2014). The primary mechanism of its antidepressant activity is through modulation of the hypothalamic-pituitary-adrenal (HPA) axis, helping to regulate cortisol secretion and improve the stress response. Additionally, Tulsi enhances monoaminergic neurotransmission, particularly by influencing serotonin and dopamine levels, which are crucial in mood stabilization. The herb also boosts brain-derived neurotrophic factor (BDNF) expression and reduces oxidative stress in the hippocampus, thereby improving neuroplasticity and emotional resilience. Preclinical and clinical studies demonstrate the antidepressant potential of holy basil. In rodent models of depression, Tulsi extracts have shown a

significant reduction in immobility time during forced swim tests, indicating behavioral reversal of despair. These findings were supported by neurochemical evidence of increased serotonin and dopamine concentrations in the brain. Clinically, a randomized, double-blind, placebo-controlled trial demonstrated that administration of *O. sanctum* leaf extract (500 mg/day) for 60 days significantly improved symptoms of mild to moderate depression, stress, and anxiety in adults, along with enhanced cognition and sleep quality. Tulsi also improved quality-of-life indices and reduced serum cortisol levels, indicating regulation of the stress response system. Importantly, Tulsi is considered safe for long-term use, with an excellent tolerability profile and no significant sedative or addictive effects. Its ability to simultaneously reduce stress, regulate neurotransmitters, and enhance mental clarity makes holy basil a highly effective botanical candidate for managing depression, particularly when associated with stress, anxiety, fatigue, or sleep disturbances (Bhattacharyya *et al*., 2008).

3. Discussion

The reviewed medicinal plants demonstrate compelling antidepressant potential through diverse yet complementary mechanisms that address core pathophysiological elements of depression. Most herbs exhibit monoaminergic enhancement (serotonin, dopamine, norepinephrine reuptake inhibition or receptor modulation), confirming the enduring relevance of this classical hypothesis while extending it through novel pathways. GABAergic modulation predominates among anxiolytic herbs (Kava, Valerian, Passion flower, Lavender, Lemon balm), explaining their particular efficacy in mixed anxiety-depression states affecting 50-60% of depressed patients. HPA axis normalization emerges as a consistent adaptogenic effect across *Rhodiola,* Ashwagandha, Holy basil, *Schisandra,* and *Centella*, addressing chronic stress, a primary depression trigger and treatment resistance factor. Neuroplasticity restoration *via* BDNF upregulation represents a particularly promising convergence, observed in Bacopa, Curcumin, Ginkgo, Centella, and *Schisandra*. This mechanism may explain their cognitive benefits beyond mood improvement, addressing the neuropsychological deficits characteristic of melancholic and geriatric depression. Anti-inflammatory and antioxidant actions (Curcumin, Saffron, Ginkgo, Bacopa) target the cytokine hypothesis, offering rationale for efficacy in inflammation-associated depression subtypes including treatment-resistant and somatic symptom variants.

Clinical translation reveals patterns favoring mild-to-moderate depression, where effect sizes frequently match SSRIs with superior tolerability. St. John's Wort, Saffron, and *Rhodiola* demonstrate the strongest RCT evidence, while *Bacopa* and Ashwagandha excel in stress-related depression with cognitive comorbidity. *Mucuna's* unique dopaminergic mechanism positions it for anhedonic/psychomotor retarded subtypes, though clinical data remains preliminary. Therapeutic advantages include rapid onset (many herbs effective within 1-2 weeks versus 4-6 for SSRIs), multitargeting reducing polypharmacy needs, and minimal sexual dysfunction/sedation/weight gain. Safety concerns warrant consideration: St. John's Wort's CYP450 induction mandates drug interaction vigilance; Kava requires noble variety/root-only extracts; high-dose Saffron risks toxicity. Bioavailability challenges (Curcumin, *Bacopa*) necessitate advanced delivery systems. Limitations include publication bias toward positive Asian studies, variable extract standardization, and paucity of head-to-head trials versus psychotherapy or lifestyle interventions. Western regulatory caution reflects historical hepatotoxicity episodes (Kava) rather than current evidence with quality-controlled extracts.

Clinical implications favor stratified phytotherapy: GABAergic herbs for anxious-restless presentations; dopaminergic adaptogens for fatigue/apathy; serotonergic extracts for classic melancholia; anti-inflammatory agents for somatic/metabolic depression. Sequential integration initiating monotherapy then augmenting per response optimizes outcomes while minimizing interactions. Future research priorities include standardized extract multicenter RCTs, pharmacogenomic predictors of response, comparative effectiveness versus psychotherapy, and long-term maintenance studies. These botanicals represent evidence-based alternatives fulfilling unmet needs in depression management: patients intolerant to synthetics, mild-moderate cases preferring natural approaches, and augmentation strategies for partial responders. Their multi-mechanism profiles align with depression's etiological heterogeneity, supporting precision phytomedicine paradigms.

4. Conclusion

Depression is a multifactorial disorder with complex pathophysiology involving neurotransmitter imbalances, HPA axis dysregulation, neuroinflammation, and impaired neuroplasticity, contributing to significant global morbidity and functional impairment. The reviewed medicinal plants demonstrate robust antidepressant potential through multi-targeted mechanisms that align with these pathophysiological processes. Monoamine modulation, GABAergic enhancement, HPA axis normalization, BDNF-mediated neuroplasticity restoration, and antioxidant and anti-inflammatory effects collectively underpin their therapeutic efficacy. Clinical evidence suggests that several botanicals are effective for mild-to-moderate depression, often producing outcomes comparable to conventional antidepressants while offering improved tolerability, faster onset of action, and lower risk of adverse effects. Certain phytochemicals may also provide cognitive benefits and address specific depressive subtypes, including stress-related, anhedonic, or inflammation-associated presentations. Despite these advantages, limitations persist, including variability in extract standardization, bioavailability issues, potential herb-drug interactions, and a paucity of long-term, multicenter randomized trials. Overall, plant-based interventions represent a valuable adjunctive or alternative approach for depression management, particularly in patient's intolerant to pharmacotherapy or seeking natural remedies. Future research focusing on standardized formulations, pharmacogenomic-guided therapy, and long-term safety is essential to fully integrate phytotherapy into evidence-based clinical practice.

Availability of data and material

All data are provided within the manuscript.

Authorship contribution statement

Bushra G. Mohammed: Contributed to conceptualization, data curation, investigation, methodology, supervision, validation, and visualization of the study. **Mahnoor Fatima**: Contributed to writing the original draft, reviewing and editing the manuscript, software handling, project administration, and methodology. **Shaika Razia**: Contributed to writing the original draft, reviewing and editing the manuscript, software handling, project administration, and methodology.

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All authors gave their full consent for publication and submission to this journal.

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