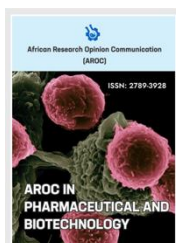




REVIEW ARTICLE

Exploring the Role of Phytochemicals in Managing Depression: Mechanisms, Therapeutic Potential, and Future Directions

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ABSTRACT

Background: Depression is a globally prevalent psychiatric disorder, and while conventional pharmacotherapies have transformed care, they are often limited by delayed onset, suboptimal efficacy, and side effects. Emerging evidence links chronic inflammation, oxidative stress, HPA axis dysregulation, neurotrophic deficits, and gut-brain axis disturbances to Major Depressive Disorder (MDD) pathophysiology. In this context, phytochemicals bioactive plant compounds show promise as adjuncts or alternatives. This review explores major phytochemical classes (flavonoids, alkaloids, terpenoids, saponins, lignans, glycosides), highlighting their antidepressant mechanisms, including monoaminergic modulation, anti-inflammation, antioxidant effects, neuroplasticity enhancement (via BDNF), HPA axis regulation, and gut microbiota influence. Notable agents like curcumin, resveratrol, berberine, ashwagandha, and Rhodiola rosea have demonstrated efficacy in preclinical and clinical settings. Traditional medical systems also utilize synergistic multi-herb formulations. Despite their potential, challenges such as poor bioavailability, lack of standardization, potential herb-drug interactions, and regulatory inconsistencies impede clinical translation. Future directions involve personalized phytomedicine, bioavailability-enhancing technologies, systems biology, and large-scale randomized controlled trials to establish efficacy and safety. Overall, phytochemicals offer a scientifically grounded and patient-friendly avenue for advancing depression therapeutics.

Keywords: Phytochemicals; Depression; Neuroinflammation; Brain-Derived Neurotrophic Factor (BDNF); Monoaminergic Modulation; Gut-Brain Axis

Received: 18 April 2025, Revised: 28 June 2025, Published: July 2025

Citation: Balogun, S. M., Ajen, M. U., Igboke, S. O., Alugbo, S. U., Asogwa, F. O., & Agboola, A. R. (2025). *Exploring the role of phytochemicals in managing depression: Mechanisms, therapeutic potential, and future directions*. AROC in Pharmaceutical and Biotechnology, 5(2), 1-17. <https://doi.org/10.53858/arocpb05020117>

1. Introduction

Depression, clinically referred to as Major Depressive Disorder (MDD), is a pervasive and debilitating psychiatric condition with a substantial global footprint. According to the World Health Organization (2023), depression is now the leading cause of disability worldwide, affecting more than 280 million individuals across all age groups. This burden is not only personal but also systemic, contributing to lost productivity, increased healthcare expenditures, and significant societal costs (GBD 2019 Mental Disorders Collaborators, 2022).

The condition manifests through a constellation of symptoms, including persistent sadness, anhedonia (loss of interest or pleasure in normally rewarding activities), fatigue, diminished concentration, altered appetite or sleep, psychomotor changes, and, in severe cases, suicidal ideation or behavior (American Psychiatric Association, 2022; Malhi & Mann, 2018). While the etiology of depression is multifactorial, encompassing genetic, biological, psychological, and environmental components, the standard of care has largely revolved around pharmacological interventions that modulate monoaminergic neurotransmission. Commonly prescribed drugs include:

Selective Serotonin Reuptake Inhibitors (SSRIs) such as fluoxetine and sertraline, Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs) like venlafaxine and duloxetine, Tricyclic Antidepressants (TCAs) such as amitriptyline, and Monoamine Oxidase Inhibitors (MAOIs) including phenelzine and tranylcypromine (Gelenberg et al., 2010; Cipriani et al., 2018; Machado et al., 2006). Although these medications have revolutionized psychiatric care, they are not without significant limitations. Adverse effects—including sexual dysfunction, gastrointestinal upset, insomnia, emotional blunting, and weight gain—are common and often lead to poor adherence (Fava et al., 2018; Serretti & Chiesa, 2009).

Furthermore, these medications exhibit a delayed onset of action, typically requiring 2–6 weeks to achieve clinical efficacy. This delay can be particularly distressing for patients in acute distress or at risk for suicide (Machado-Vieira et al., 2010; Papakostas, 2006). Crucially, a substantial subset of patients (~30–40%) are classified as treatment-resistant, meaning they fail to respond adequately to at least two different antidepressant regimens (Rush et al., 2006). For these individuals, the therapeutic arsenal remains limited, prompting an urgent need for novel and multimodal therapeutic strategies that address both symptom severity and biological complexity.

Importantly, growing evidence indicates that environmental toxicants—such as endocrine-disrupting chemicals, heavy metals, pesticides, and persistent organic pollutants—play a critical role in the development of chronic diseases including metabolic syndrome, cancer (Onah et al., 2024; Edema et al., 2023; Ogunjobi et al., 2025; Omiyale et al., 2024a, b), and neuropsychiatric conditions like depression. These toxicants can induce systemic oxidative stress, impair mitochondrial function, trigger low-grade chronic inflammation, and dysregulate hormonal and neurotransmitter pathways, thereby exacerbating disease susceptibility (Ogunlakin et al., 2024). In this context, medicinal plants have garnered attention for their chemopreventive and therapeutic potential.

Many phytochemicals derived from these plants act as natural detoxifiers, restoring redox balance, modulating inflammatory cytokines, supporting mitochondrial health, and counteracting the molecular damage induced by toxic exposures. Thus, beyond their nutritive value, medicinal plants serve a critical protective role in mitigating toxicant-induced health deterioration. Given these shortcomings in conventional antidepressant therapy and the broader context of environmental contributors to neuropsychiatric illness, there has been a resurgence of interest in natural products, particularly phytochemicals—biologically active, non-nutritive compounds derived from plants. These compounds are traditionally found in fruits, vegetables, herbs, teas, roots, and medicinal plants, and have been used for centuries in various ethnomedical systems including Ayurveda, Traditional Chinese Medicine (TCM), and Kampo.

Modern pharmacological research has identified numerous phytochemicals with neuroprotective, anti-inflammatory, antioxidant, and neurotrophic properties—mechanisms that directly counter the pathophysiological processes implicated in depression and environmentally induced disease states (Ogunlakin et al., 2025a; Ogunlakin et al., 2025b; Oluyemis et al., 2021; Adegbesan et al., 2021; Ogunlabi et al., 2020; Ogunlakin et al., 2024). Notably, several phytochemicals regulate monoamine levels (serotonin, dopamine, norepinephrine), suppress neuroinflammation via cytokine inhibition, combat oxidative stress through reactive oxygen species (ROS) scavenging, enhance neuroplasticity by upregulating brain-derived neurotrophic factor (BDNF), and influence the gut–brain axis, thereby modulating mood through microbiota-derived metabolites.

Furthermore, phytochemicals tend to have low toxicity profiles, and many are available as dietary supplements or functional foods, which enhances their accessibility and patient acceptability (Ogunlakin et al., 2025c). Some—such as curcumin (turmeric), berberine, resveratrol, ashwagandha, and St. John's Wort—have already undergone preliminary clinical testing for mood disorders, with encouraging results.

This review aims to systematically explore the mechanistic foundations, experimental evidence, and clinical applications of phytochemicals in the context of depression. By synthesizing data from molecular biology, preclinical pharmacology, and human trials, we seek to clarify the potential of these natural agents to serve as either standalone treatments or adjunctive therapies in comprehensive depression management. The goal is to foster a deeper understanding of how nature-derived compounds can be scientifically harnessed to combat one of the most pressing global mental health challenges of our time.

2. Pathophysiology of Depression

Understanding the pathophysiological underpinnings of depression is pivotal for evaluating how phytochemicals exert their therapeutic benefits. Major Depressive Disorder (MDD) is a multifactorial psychiatric condition influenced by neurochemical imbalances, endocrine dysfunction, immune activation, oxidative stress, genetic predispositions, and environmental factors such as trauma and chronic stress (Figure 1). Contemporary neuroscience has moved beyond the single-neurotransmitter theory, instead embracing a systems-level approach involving complex interdependent biological circuits.

2.1. Monoaminergic Hypothesis

The monoaminergic hypothesis has served as the cornerstone of depression research since the 1950s. This model posits that the depletion of monoamine neurotransmitters—namely serotonin (5-hydroxytryptamine or 5-HT), dopamine (DA), and norepinephrine (NE)—is central to the development of depressive symptoms (Hirschfeld, 2000). These

neurotransmitters regulate mood, motivation, attention, sleep, and cognition.

Serotonin is primarily synthesized in the raphe nuclei of the brainstem and is involved in regulating mood, anxiety, and circadian rhythm. Deficiency in 5-HT is associated with rumination, pessimism, and suicidal ideation. Dopamine plays a role in motivation, reward processing, and pleasure. Reduced dopaminergic signaling contributes to anhedonia and psychomotor retardation.

Norepinephrine affects arousal and vigilance; deficits can lead to fatigue, reduced concentration, and psychomotor slowing. Although SSRIs, SNRIs, and other monoaminergic antidepressants aim to restore neurotransmitter balance, their delayed onset of action (typically 2–6 weeks) and partial efficacy (approximately 30–40% non-response rate) suggest that monoamine imbalance is a downstream phenomenon rather than the sole causative factor (Krishnan & Nestler, 2008). This has encouraged researchers to explore alternative and complementary mechanisms.

2.2. Hypothalamic–Pituitary–Adrenal Axis Dysregulation

The HPA axis is the central stress response system in the body. Under stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary gland to secrete adrenocorticotrophic hormone (ACTH), leading to cortisol release from the adrenal cortex. While acute activation is adaptive, chronic stress leads to sustained HPA axis activation and glucocorticoid resistance, damaging brain structures such as the hippocampus and prefrontal cortex.

Elevated cortisol levels are a hallmark finding in many individuals with MDD and are associated with: Reduced hippocampal volume and neurogenesis, Impaired feedback inhibition of the HPA axis Increased anxiety and sleep disturbances. Notably, glucocorticoid-induced suppression of BDNF contributes to structural and functional deficits in the brain. Antidepressants and phytochemicals that normalize cortisol levels or enhance glucocorticoid receptor sensitivity often demonstrate efficacy in reversing depressive-like behaviors (Pariante & Lightman, 2008).

2.3. Neuroinflammation

A growing body of evidence implicates systemic and central nervous system (CNS) inflammation in the pathogenesis of depression. Pro-inflammatory cytokines such as interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and interferon-gamma (IFN- γ) are consistently elevated in both the peripheral blood and cerebrospinal fluid (CSF) of patients with Major Depressive Disorder (MDD) (Miller & Raison, 2016). These cytokines contribute to depressive symptomatology through multiple pathways. They induce a constellation of symptoms collectively known as “sickness behavior,” which includes fatigue, social withdrawal, reduced

motivation, and cognitive impairments—features that overlap significantly with clinical depression.

Additionally, inflammatory cytokines interfere with monoamine neurotransmission by activating the enzyme indoleamine 2,3-dioxygenase (IDO). This enzyme diverts tryptophan—an essential precursor for serotonin—away from serotonin synthesis and toward the kynurenine pathway, leading to the accumulation of neuroactive and potentially neurotoxic metabolites such as quinolinic acid, which further exacerbates neuroinflammation and excitotoxicity. Moreover, elevated inflammatory mediators can disrupt the integrity of the blood–brain barrier (BBB), facilitating the infiltration of peripheral immune cells and additional cytokines into the brain parenchyma, thereby amplifying local inflammation.

Collectively, this inflammatory model of depression provides a mechanistic link between chronic inflammatory conditions—such as autoimmune diseases, obesity, and metabolic syndrome—and mood disorders. It also forms a compelling rationale for the use of anti-inflammatory and immunomodulatory agents, including several phytochemicals, in the management of depression.

2.4. Oxidative Stress and Mitochondrial Dysfunction

Depression is also characterized by an imbalance between pro-oxidants and antioxidants, resulting in oxidative stress. Elevated levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) damage cellular components—proteins, lipids, and DNA—particularly in vulnerable brain regions like the hippocampus and prefrontal cortex (Salim, 2014). Concurrently, mitochondrial dysfunction impairs ATP production, increasing susceptibility to apoptosis and neurodegeneration. Markers such as Lipid peroxidation (malondialdehyde, MDA), DNA oxidation (8-hydroxy-2'-deoxyguanosine, 8-OHdG), decreased antioxidant enzymes (SOD, catalase, glutathione peroxidase) are elevated in MDD patients. These findings support the therapeutic relevance of phytochemicals with antioxidant properties, such as flavonoids, curcuminoids, and polyphenols.

2.5. Neurotrophic Hypothesis

The neurotrophic hypothesis posits that depression is associated with decreased expression of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF), which is crucial for neuronal growth and differentiation, synaptic plasticity, dendritic arborization and long-term potentiation (LTP). BDNF is predominantly synthesized in the hippocampus and prefrontal cortex—areas heavily implicated in emotion regulation and cognition. Chronic stress and elevated cortisol suppress BDNF expression, while antidepressants and exercise promote its upregulation (Duman & Monteggia, 2006). Phytochemicals such as resveratrol, ginsenosides, apigenin, and berberine have been shown to enhance BDNF and activate

TrkB-CREB signaling pathways, leading to improved neuronal resilience and mood regulation.

2.6. Gut–Brain Axis

The gut–brain axis (GBA) is a bidirectional communication system involving the CNS, enteric nervous system (ENS), immune system, and gut microbiota. This axis influences neurodevelopment, behavior, and mood via: Microbial metabolites (e.g., short-chain fatty acids like butyrate), Tryptophan metabolism and serotonin biosynthesis, Modulation of the immune system and inflammatory pathways, Vagal nerve signaling. Dysbiosis, or an imbalance in gut microbial composition, has been associated with depressive symptoms. Germ-free mice and antibiotic-treated rodents exhibit increased anxiety-like and depressive behaviors, which can be reversed with probiotics or fecal microbiota transplantation (Foster & Neufeld, 2013). Phytochemicals that exert prebiotic effects—such as polyphenols, berberine, and quercetin—may restore microbial homeostasis and improve mood via GBA modulation. Antioxidant effects involve scavenging reactive oxygen species and boosting endogenous defense enzymes. HPA axis regulation is achieved by reducing cortisol levels and normalizing stress responses. Several compounds also influence the gut–brain axis by improving microbiota balance and producing beneficial metabolites, while some interact directly with GABAergic, NMDA, and cannabinoid receptors to support mood stabilization.

inflammatory actions include suppression of pro-inflammatory cytokines and NF- κ B.

3. Phytochemicals: Overview and Classification

Phytochemicals are naturally occurring bioactive compounds found in plants that contribute to their color, flavor, and resistance to pathogens. Although not classified as essential nutrients like vitamins and minerals, phytochemicals play a significant role in promoting human health and preventing diseases, including cancer, cardiovascular disorders, metabolic syndromes, and neuropsychiatric illnesses such as depression (Liu, 2004).

Phytochemicals are broadly categorized based on their chemical structure and biosynthetic origin. The major classes include flavonoids, alkaloids, terpenes and terpenoids, polyphenols, saponins, glycosides, and lignans (Figure 2, Table 1). Many of these compounds are found in common herbs, spices, fruits, vegetables, and medicinal plants.

Table 1: Classification of Phytochemicals

Class	Examples	Sources	Key Actions
Flavonoids	Quercetin, kaempferol, apigenin	Onions, apples, parsley, tea	Antioxidant, anti-inflammatory
Alkaloids	Berberine, harmine	Goldenseal, ayahuasca	Neuroprotective, MAO inhibition
Terpenoids	Limonene, ginsenosides	Citrus, ginseng	Antidepressant, adaptogenic
Phenolic Acids	Ferulic acid, caffeic acid	Berries, coffee	Neuroprotective, anti-inflammatory
Lignans	Secoisolariciresinol	Flaxseed, sesame	Antioxidant, estrogenic activity
Saponins	Bacosides, ginsenosides	Bacopa, ginseng	HPA modulation, BDNF activation

The versatility of phytochemicals lies in their ability to modulate multiple targets implicated in the pathophysiology of depression, including neurotransmitters, inflammatory mediators, oxidative stress pathways, and neurotrophic signaling (Panche, Diwan, & Chandra, 2016).

4. Flavonoids and Polyphenols in Depression

Among the phytochemicals, flavonoids and polyphenols have received the most scientific attention for their neuropsychological effects (Table 2; figure 2). These compounds, characterized by their polyphenolic structure, exert powerful antioxidant, anti-inflammatory, and neuroprotective effects.

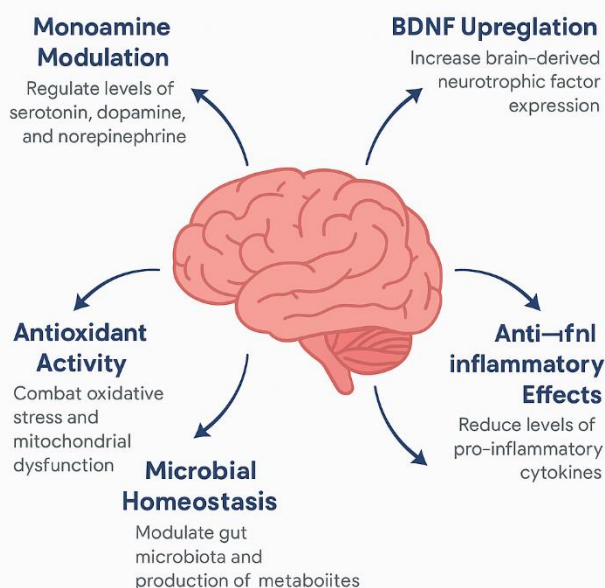


Figure 1. Mechanisms of Action of Phytochemicals in Depression: This figure illustrates how phytochemicals alleviate depressive symptoms through multiple interconnected pathways. They modulate monoaminergic systems by enhancing serotonin, dopamine, and norepinephrine levels. Many promote neurotrophic signaling by upregulating BDNF and activating TrkB-CREB cascades. Anti-

4.1. Quercetin

Quercetin is a flavonol found in apples, onions, and tea. In rodent models, quercetin has been shown to reverse depressive-like behaviors induced by chronic stress via multiple mechanisms, including inhibition of monoamine oxidase (MAO), reduction of pro-inflammatory cytokines, and enhancement of hippocampal BDNF expression (Samad, Haleem, & Haleem, 2018). Quercetin also acts on the gut-brain axis by modulating microbiota composition, potentially reducing systemic inflammation and promoting serotonergic tone (Lin et al., 2019).

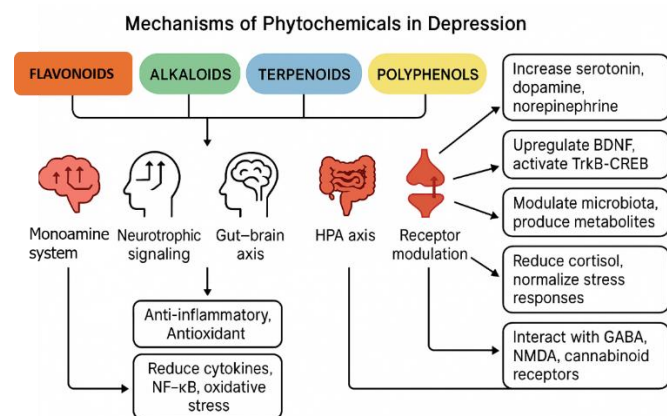


Figure 2: A schematic diagram illustrating the mechanistic pathways through which different classes of phytochemicals exert antidepressant effects. Flavonoids, alkaloids, terpenoids, lignans, saponins, and polyphenols modulate key neurobiological targets including monoamine neurotransmission, neurotrophic signaling (e.g., BDNF/TrkB), HPA axis regulation, neuroinflammation, oxidative stress pathways, and gut-brain axis signaling. These mechanisms converge to enhance neuroplasticity, reduce neuroinflammatory burden, stabilize mood, and promote stress resilience, collectively contributing to their therapeutic potential in depression.

4.2. Kaempferol

Kaempferol, abundant in kale, spinach, and tea, displays antidepressant-like properties in chronic mild stress (CMS) models by suppressing oxidative stress and pro-inflammatory pathways. It is known to modulate NF- κ B signaling and upregulate BDNF and CREB expression (Liao et al., 2017).

4.3. Naringenin

Naringenin, a citrus flavonoid, exhibits antidepressant activity via serotonergic, dopaminergic, and GABAergic pathways. In murine models, it has been shown to decrease immobility time in the tail suspension test and enhance brain monoamine levels (Golechha, Bhatia, & Arya, 2012).

4.4. Apigenin

Apigenin, found in parsley, chamomile, and celery, has demonstrated anxiolytic and antidepressant effects. It

enhances GABA receptor binding and attenuates the neuroinflammatory response in LPS-induced depression models (Nakazawa et al., 2003).

4.5. Epigallocatechin Gallate (EGCG)

EGCG, the most abundant catechin in green tea, exhibits potent antidepressant effects. It is known to enhance dopamine and serotonin turnover, reduce oxidative damage, and modulate HPA axis responsiveness (Chhilar & Dhingra, 2013). Additionally, EGCG influences synaptic plasticity by increasing BDNF expression and CREB phosphorylation.

4.6. Resveratrol

Resveratrol, a polyphenol found in grapes, red wine, and peanuts, activates SIRT1 and the AMPK pathway. It reduces neuroinflammation and oxidative damage and promotes hippocampal neurogenesis (Liu et al., 2014). Clinical trials have reported mood improvements in postmenopausal women and stressed individuals after resveratrol supplementation (Bo et al., 2013).

4.7. Mechanisms of Action

The therapeutic efficacy of flavonoids and polyphenols in depression is attributed to their multifaceted biological mechanisms, which target the core pathophysiological domains of the disorder. One of the primary mechanisms involves monoamine modulation, where several flavonoids have been shown to inhibit monoamine oxidase A and B (MAO-A/B) enzymes. This inhibition leads to increased synaptic availability of critical neurotransmitters such as serotonin and dopamine, which are frequently depleted in depressive states. In addition to enhancing neurotransmission, flavonoids exhibit robust antioxidant activity by scavenging reactive oxygen species (ROS) and upregulating the body's endogenous antioxidant defenses, including superoxide dismutase (SOD) and catalase. This action helps mitigate oxidative damage in neural tissues, particularly in the hippocampus and prefrontal cortex.

Flavonoids and polyphenols also exert potent anti-inflammatory effects, primarily through the downregulation of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6). By attenuating neuroinflammation, these compounds can restore neurotransmitter balance and neuronal integrity. Another critical pathway involves neurotrophic support, where flavonoids activate the BDNF-TrkB-CREB signaling cascade, promoting neurogenesis, synaptic plasticity, and long-term potentiation—all of which are impaired in Major Depressive Disorder (MDD).

Furthermore, these phytochemicals play a role in regulating the hypothalamic-pituitary-adrenal (HPA) axis, often disrupted in chronic stress and depression. By normalizing levels of corticosterone and adrenocorticotrophic hormone (ACTH) in animal stress models, flavonoids help restore endocrine balance. Their influence on synaptic plasticity is also notable, with evidence suggesting modulation of both N-methyl-D-

aspartate (NMDA) and gamma-aminobutyric acid (GABA) receptor systems, which are crucial for mood regulation and cognitive function. Lastly, recent studies have highlighted the impact of flavonoids on the gut–brain axis. These compounds contribute to favorable shifts in gut microbiota composition and enhance the production of short-chain fatty acids (SCFAs) such as butyrate, which are known to exert anti-inflammatory and neuroprotective effects through both direct and vagally mediated pathways. Collectively, these diverse but interrelated mechanisms underscore the promise of flavonoids and polyphenols as multimodal agents in the management of depression.

Table 2: Summary of Flavonoids and Polyphenols in Depression

Phytochemical	Source	Main Mechanism
Quercetin	Apples, onions, tea	MAO inhibition, ↑BDNF, anti-inflammatory
Kaempferol	Kale, spinach, tea	↑BDNF, ↓NF-κB, antioxidant
Naringenin	Citrus fruits	↑5-HT, ↑DA, GABA modulation
Apigenin	Parsley, chamomile	GABA binding, anti-inflammatory
EGCG	Green tea	↑BDNF, HPA modulation, antioxidant
Resveratrol	Grapes, red wine	↑SIRT1, ↓neuroinflammation, ↑neurogenesis

5. Alkaloids in Depression: Pharmacological Significance

Alkaloids represent a structurally diverse class of nitrogen-containing natural compounds that exert profound effects on the central nervous system (CNS). Widely distributed in plants, many alkaloids—such as morphine, codeine, and atropine—have been utilized in modern medicine for their analgesic and neuromodulatory properties (Table 3). In the context of depression, an expanding body of evidence highlights the antidepressant-like potential of several plant-derived alkaloids, which function through a combination of mechanisms, including modulation of monoamine neurotransmission, enhancement of neurotrophic signaling, suppression of neuroinflammation, and regulation of gut–brain interactions (Heinrich et al., 2020).

5.1. Berberine

Berberine, an isoquinoline alkaloid derived from plants such as *Berberis vulgaris*, *Coptis chinensis*, and *Hydrastis canadensis*, has shown strong antidepressant effects in various preclinical models. Its primary mechanism involves the inhibition of monoamine oxidase A (MAO-A), which leads to increased brain levels of serotonin, dopamine, and norepinephrine, thereby improving mood and affective balance (Kulkarni & Dhir, 2008). In addition, berberine promotes the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus, facilitating neurogenesis and synaptic remodeling (Zhang et

al., 2015). Its anti-inflammatory properties are evidenced by its ability to suppress microglial activation and downregulate key inflammatory mediators such as IL-6, TNF-α, and NF-κB (Fan et al., 2017).

Importantly, berberine also interacts with the gut microbiome, restoring microbial balance and reducing endotoxemia-induced depressive behaviors (Zhang et al., 2020). In models of chronic unpredictable mild stress (CUMS) and lipopolysaccharide (LPS)-induced depression, berberine significantly reverses both behavioral and neurochemical abnormalities.

5.2. Harmine

Harmine is a β-carboline alkaloid found in *Banisteriopsis caapi*, the principal component of the traditional Amazonian brew ayahuasca. Harmine acts as a reversible inhibitor of MAO-A, leading to increased availability of serotonin and norepinephrine in the brain (Fortunato et al., 2009). Beyond its monoaminergic action, harmine enhances BDNF signaling through the activation of TrkB and CREB pathways in the hippocampus, contributing to improved neuroplasticity and resilience to stress (Dakic et al., 2016).

Furthermore, it has been shown to exert anti-inflammatory effects by downregulating the expression of TNF-α and IL-1β in the prefrontal cortex (dos Santos et al., 2017). Preclinical studies using rodent models consistently demonstrate harmine's ability to reduce immobility time in behavioral despair tests, while observational studies on ayahuasca users report rapid and enduring antidepressant responses (Palhano-Fontes et al., 2019).

5.3. Piperine

Piperine, a major pungent alkaloid in black pepper (*Piper nigrum*), is recognized for its role in enhancing the bioavailability of co-administered phytochemicals, including curcumin and resveratrol. On its own, piperine has demonstrated antidepressant-like effects in animal studies, attributed to its modulation of serotonergic and dopaminergic systems within the hippocampus and frontal cortex (Kumar et al., 2013). It also exhibits antioxidant and anti-inflammatory properties, contributing to the reduction of oxidative stress and inflammatory load in the CNS (Bang et al., 2009). In addition, piperine appears to support GABAergic neurotransmission, which may explain its mild anxiolytic and mood-stabilizing effects (Meena et al., 2019). By enhancing gut barrier function and reducing systemic inflammation, piperine further promotes gut–brain axis homeostasis.

5.4. Mitragynine

Mitragynine is the principal indole alkaloid found in *Mitragyna speciosa* (kratom), a plant native to Southeast Asia. It binds to opioid receptors, functioning as a partial agonist at μ-opioid sites, thereby producing analgesic and mood-elevating effects. Although its use is controversial due to potential dependence and regulatory restrictions, mitragynine has shown antidepressant-like properties at lower doses. It enhances

serotonin and dopamine turnover and may exhibit rapid-onset effects similar to ketamine in some models (Yusoff et al., 2016; Vijeepallam et al., 2019). Nonetheless, concerns about abuse liability have limited its therapeutic development in Western pharmacology.

5.5. Other Promising Alkaloids

Several additional alkaloids have shown early promise in preclinical investigations. Tetrahydropalmatine, isolated from *Corydalis yanhusuo*, modulates dopamine D2 receptors and exhibits sedative and mood-elevating properties. Magnoflorine, found in *Magnolia officinalis*, exerts anxiolytic effects and suppresses HPA axis hyperactivation. Sanguinarine, a benzophenanthridine alkaloid from *Sanguinaria canadensis*, reduces inflammation by inhibiting NF- κ B signaling. While these agents are less studied in the context of depression, their pharmacological profiles suggest potential utility as adjuncts in mood regulation.

5.6. Mechanisms of Action Summary

The antidepressant effects of alkaloids are mediated through several converging biological pathways. These compounds often inhibit MAO-A, resulting in elevated levels of monoamines such as serotonin, dopamine, and norepinephrine in the brain. Simultaneously, they promote neurotrophic support by upregulating BDNF and activating associated signaling pathways like TrkB and CREB, which are essential for neuroplasticity and synaptic maintenance. Many alkaloids exhibit anti-inflammatory actions by reducing the expression of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and suppressing microglial activation.

Additionally, some alkaloids help regulate the HPA axis by decreasing circulating levels of ACTH and cortisol, thereby mitigating the detrimental effects of chronic stress. Modulation of synaptic plasticity and receptor systems—particularly GABA and glutamate—is also a common mechanism. Finally, several alkaloids influence the gut microbiota, contributing to improved gut-brain communication and reduced systemic inflammation.

Overall, the multimodal pharmacology of plant-derived alkaloids enhances their appeal as potential therapeutics in depression, particularly in treatment-resistant or comorbid cases. However, careful consideration of their safety profiles, pharmacokinetics, and potential for drug interactions remains essential before widespread clinical implementation.

6. Terpenes and Terpenoids: Neuroactive Potential in Depression

Terpenes and terpenoids represent one of the largest and most chemically diverse classes of phytochemicals, comprising compounds derived from isoprene units. Found abundantly in aromatic herbs, resins, and essential oils, they contribute to the characteristic scents of many medicinal and culinary plants (Table 4). Beyond their aromatic appeal, a growing body of literature supports their therapeutic relevance in neuropsychiatric disorders.

Terpenes have been shown to possess neuroprotective, antioxidant, anti-inflammatory, anxiolytic, and antidepressant properties. Due to their relatively small size and lipophilic nature, many terpenes can cross the blood-brain barrier, allowing them to directly modulate central nervous system (CNS) pathways relevant to mood regulation (Russo, 2011). These attributes position terpenes as promising candidates for complementary and integrative approaches to depression therapy.

6.1. Limonene

Limonene is a widely studied monoterpene primarily found in citrus fruits and their peels. In experimental models of depression, limonene has been shown to modulate central monoaminergic systems, enhancing both serotonergic and dopaminergic signaling. This neuromodulatory action contributes to its observed mood-elevating properties. In addition, limonene exhibits potent anti-inflammatory effects by downregulating cytokines such as IL-1 β and TNF- α , key players in the neuroinflammatory cascade associated with major depressive disorder.

Importantly, limonene enhances hippocampal BDNF levels, promoting neurogenesis and synaptic resilience. Stress-induced elevations in plasma corticosterone are also attenuated by limonene treatment, indicating a role in regulating hypothalamic-pituitary-adrenal (HPA) axis function. Inhalational studies in rodents and small clinical trials have consistently demonstrated its antidepressant potential through multiple convergent mechanisms (Komori et al., 1995; Chen et al., 2013; Li et al., 2018).

Table 3: Summary of Alkaloids in Depression

Alkaloid	Plant Source	Main Mechanisms
Berberine	Berberis spp., Coptis chinensis	↑ BDNF, MAO-A inhibition, anti-inflammatory, gut-brain modulation
Harmine	Banisteriopsis caapi	MAO-A inhibition, ↑ BDNF, anti-inflammatory
Piperine	Piper nigrum (black pepper)	↑5-HT/DA, GABAergic, antioxidant, bioenhancer
Mitragynine	Mitragyna speciosa (kratom)	μ -opioid modulation, ↑ monoamines, rapid effects
Tetrahydropalmatine	Corydalis yanhusuo	Dopamine D2 modulation, sedative, neuroprotection

Their use in aromatherapy, dietary supplements, and traditional herbal medicine suggests broad accessibility and safety with proper dosing.

6.2. Linalool

Linalool, a naturally occurring terpene alcohol, is found in a wide array of aromatic plants including lavender (*Lavandula angustifolia*), coriander, and basil. It is one of the most extensively studied terpenes for its anxiolytic and antidepressant-like effects. The primary mechanism of linalool involves modulation of GABAergic neurotransmission, as it enhances the function of GABA-A receptors, producing calming and mood-stabilizing effects. Linalool also elevates central serotonin and dopamine levels, further supporting its antidepressant profile. Moreover, it possesses strong antioxidant activity, reducing lipid peroxidation markers such as malondialdehyde (MDA) and upregulating antioxidant enzymes like superoxide dismutase (SOD).

In behavioral paradigms, linalool reduces immobility times in forced swim and tail suspension tests, which are commonly used to assess antidepressant efficacy in rodents. The clinical formulation Silexan, a standardized lavender oil preparation rich in linalool, is approved in several European countries as a phytomedicine for the treatment of generalized anxiety and subthreshold depressive disorders (Linck et al., 2009; Zhang et al., 2016; Woelk & Schlafke, 2010).

6.3. Ginsenosides

Ginsenosides are the primary pharmacologically active constituents of ginseng species such as *Panax ginseng* and *Panax quinquefolius*. Structurally categorized as triterpenoid saponins, ginsenosides exhibit diverse neurobiological actions. Specific ginsenosides, including Rg1, Rb1, and Rg3, have been shown to upregulate BDNF and activate the CREB signaling cascade, thereby enhancing neurogenesis and synaptic remodeling in the hippocampus and prefrontal cortex. These compounds also modulate levels of serotonin and norepinephrine, key neurotransmitters implicated in the pathophysiology of depression.

Their anti-inflammatory and antioxidant properties further contribute to their neuroprotective effects. Additionally, ginsenosides appear to influence HPA axis activity by mitigating stress-induced corticosterone surges. Animal studies utilizing chronic stress models have confirmed their ability to reverse behavioral deficits and reduce neuroinflammatory markers (Jiang et al., 2012; Wang et al., 2015).

6.4. Curcumin

Curcumin, the principal curcuminoid of *Curcuma longa* (turmeric), exhibits characteristics of both polyphenols and terpenoids due to its hybrid chemical structure. It has been widely studied for its potent anti-inflammatory and antioxidant properties, which are directly relevant to the pathophysiology of depression. Mechanistically, curcumin suppresses pro-inflammatory mediators including NF- κ B, IL-6, and TNF- α , thus attenuating neuroinflammation. It also enhances hippocampal neuroplasticity by upregulating BDNF expression and supporting neurogenesis. Curcumin modulates monoamine levels by inhibiting monoamine oxidase-A (MAO-A), leading to

elevated serotonin and dopamine concentrations in key brain regions.

In addition to scavenging reactive oxygen species, curcumin augments the activity of endogenous antioxidant enzymes. Human trials suggest that curcumin, when used in combination with SSRIs, can significantly reduce depressive symptoms, especially in individuals with high inflammatory or oxidative stress markers (Lopresti et al., 2012; Kulkarni et al., 2008; Lopresti et al., 2015).

6.5. Other Prominent Terpenes with Antidepressant Activity

Several other terpenes have emerged as candidates for depression management. β -Caryophyllene, found in black pepper and clove, acts as a CB2 cannabinoid receptor agonist and exerts significant anti-inflammatory effects. Thymol, a phenolic monoterpene from thyme and oregano, enhances GABAergic neurotransmission and displays anxiolytic and sedative properties. α -Pinene, prevalent in pine needles and rosemary, has anti-inflammatory effects and supports cognitive function.

Carvacrol, also found in oregano, elevates serotonin and dopamine levels in the hippocampus, thereby enhancing mood. These compounds often demonstrate greater efficacy when used in synergy with other phytochemicals, suggesting the importance of the entourage effect in whole-plant therapy.

Table 4: Summary of terpenes in Depression

Terpene	Source	Main Mechanisms
Limonene	Citrus peels	$\uparrow$ 5-HT/DA, anti-inflammatory, $\uparrow$ BDNF
Linalool	Lavender, coriander	GABAergic modulation, $\uparrow$ monoamines
Ginsenosides	Ginseng root	$\uparrow$ BDNF/CREB, $\downarrow$ inflammation, $\uparrow$ 5-HT/NE
Curcumin	Turmeric	MAO inhibition, $\uparrow$ BDNF, antioxidant
β -Caryophyllene	Clove, black pepper	CB2 agonism, $\downarrow$ neuroinflammation

6.6. Mechanisms of Action Summary

Terpenes and terpenoids exert their antidepressant effects through multiple interconnected mechanisms. They regulate the synthesis, release, and receptor activity of key neurotransmitters such as serotonin, dopamine, and GABA, leading to improved mood, emotional regulation, and cognitive function. At the molecular level, these compounds inhibit pro-inflammatory transcription factors like NF- κ B and reduce the expression of cytokines implicated in neuroinflammation. Many terpenes upregulate BDNF and stimulate neuroplasticity, promoting the repair and regeneration of damaged neurons. Some terpenes, such as β -caryophyllene, interact with

components of the endocannabinoid system, including CB2 and TRPV1 receptors, further influencing emotional processing. Additionally, modulation of the HPA axis by terpenes helps normalize stress hormone levels, thereby preventing chronic cortisol elevation and its associated neurotoxic effects. Taken together, these diverse molecular actions highlight the therapeutic potential of terpenes and terpenoids in the prevention and management of depressive disorders.

7. Lignans, Saponins, and Miscellaneous Phytochemicals: Expanding the Therapeutic Frontier

While much attention has been directed toward flavonoids, alkaloids, and terpenoids in the context of depression management, other phytochemical classes—including lignans, saponins, glycosides, and coumarins—are emerging as valuable contributors to the therapeutic landscape (Table 5). These compounds exhibit a range of biological activities that converge on the neurobiological substrates of depression, such as oxidative stress, neuroinflammation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and deficits in neurotrophic signaling. In many cases, their therapeutic potential is further amplified by their inclusion in traditional medicinal systems and polyherbal preparations.

7.1. Honokiol

Honokiol, a neolignan isolated from the bark of *Magnolia officinalis*, has demonstrated potent antidepressant-like effects in both preclinical and clinical studies. It acts partly through the modulation of GABA-A receptors, thereby enhancing inhibitory neurotransmission within key brain regions associated with emotional regulation. Moreover, honokiol exhibits strong anti-inflammatory effects by downregulating pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β).

It also promotes hippocampal neurogenesis by stimulating the proliferation and differentiation of neural precursor cells. In animal models of chronic stress, honokiol administration has been associated with reduced depressive-like behaviors and increased expression of brain-derived neurotrophic factor (BDNF) in the hippocampus and prefrontal cortex.

7.2. Withanolides (Ashwagandha)

Withanolides, the principal steroidal lactones found in *Withania somnifera* (ashwagandha), are central to the herb's adaptogenic and neuroprotective properties. These compounds regulate the HPA axis by reducing cortisol secretion and restoring feedback sensitivity, which is often impaired in depression. Furthermore, they promote BDNF expression and enhance neuroplasticity, contributing to greater resilience against chronic stress. Clinical studies have demonstrated that standardized ashwagandha extracts significantly improve depressive symptomatology, as evidenced by reductions in scores on the Beck Depression Inventory (BDI) and the Perceived Stress Scale (PSS), particularly among individuals with mild to moderate depression.

7.3. Bacosides (*Bacopa monnieri*)

Bacosides, a class of saponins derived from *Bacopa monnieri*, are traditionally recognized for their cognitive-enhancing and adaptogenic effects. These compounds have been shown to alleviate depressive symptoms, improve memory, and reduce anxiety in both animal and human studies. Their antioxidant properties involve the scavenging of reactive oxygen species (ROS) and the enhancement of endogenous antioxidant enzyme systems. Bacosides also appear to increase central serotonin levels and modulate serotonin receptor activity. In chronic unpredictable mild stress (CUMS) models, bacoside A significantly improves depressive behavior and is associated with upregulation of hippocampal BDNF levels.

7.4. Silymarin

Silymarin is a flavonolignan complex extracted from *Silybum marianum* (milk thistle) and is primarily used for its hepatoprotective effects. However, it also shows promise in the neuropsychiatric domain. Silymarin weakly inhibits monoamine oxidase-A (MAO-A), leading to increased levels of serotonin, dopamine, and norepinephrine.

Additionally, it provides neuroprotection against excitotoxicity and neuroinflammation, and promotes neurogenesis through activation of extracellular signal-regulated kinase (ERK) and cyclic AMP response element-binding protein (CREB) pathways. Though less studied than other phytochemicals, silymarin's effects are particularly relevant in cases of depression secondary to chronic liver disease or systemic inflammatory states.

7.5. Rhodiola rosea

Rhodiola rosea, also known as golden root, contains active glycosides such as salidroside and rosavin that have been shown to possess adaptogenic and antidepressant effects. These compounds reduce HPA axis overactivation and attenuate cortisol responses under stress. They also enhance central monoamine levels, particularly serotonin and norepinephrine, within the hippocampus and other limbic structures.

In addition to modulating neurotransmitters, *Rhodiola* extracts improve fatigue, concentration, and mood. Clinical trials have shown that *Rhodiola* is as effective as low-dose sertraline in reducing depressive symptoms, with a lower incidence of adverse effects, making it a promising alternative or adjunct for patients intolerant to conventional medications.

7.6. Other Notable Compounds

Several other phytochemicals also warrant mention due to their emerging roles in mood regulation. Salidroside, another glycoside found in *Rhodiola rosea*, enhances central monoamine availability while reducing HPA axis overactivation. Mangiferin, a xanthonoid from mango leaves, exerts strong antioxidant and anti-inflammatory effects while enhancing BDNF expression. Ferulic acid, found in rice bran and wheat,

exhibits anti-inflammatory properties and modulates N-methyl-D-aspartate (NMDA) receptors implicated in synaptic plasticity. Tanshinone IIA, a diterpene quinone from *Salvia miltiorrhiza*, exerts both neurotrophic and anti-inflammatory effects that are relevant to neuropsychiatric resilience.

7.7. Mechanistic Insights

The antidepressant effects of lignans, saponins, glycosides, and related compounds are mediated through a wide array of molecular and cellular mechanisms. Many of these phytochemicals act as adaptogens, enhancing the body's resistance to stress by restoring HPA axis equilibrium. They also exert neuroprotective effects by preventing neuronal apoptosis and stimulating neurogenesis. At the synaptic level, these compounds activate signaling pathways involving BDNF, CREB, and ERK, which are critical for synaptic remodeling and long-term potentiation.

Monoamine modulation is another consistent feature, with increased activity of serotonin, dopamine, and norepinephrine observed in multiple models. Additionally, many of these phytochemicals inhibit pro-inflammatory mediators such as nuclear factor kappa B (NF-κB) and interleukin-6 (IL-6), while enhancing antioxidant defenses. Importantly, these compounds are often used in traditional polyherbal formulations or in conjunction with standard antidepressants, suggesting possible synergistic benefits and wider therapeutic utility.

Table 5: Summary of Lignans, Saponins in Depression

Compound	Source	Main Mechanisms
Honokiol	Magnolia bark	GABAergic, ↑ BDNF, anti-inflammatory
Withanolides	Withania somnifera (Ashwagandha)	↓ Cortisol, ↑ BDNF, adaptogenic
Bacosides	Bacopa monnieri	↑ Serotonin, antioxidant, ↑ BDNF
Silymarin	Milk thistle (Silybum marianum)	MAO inhibition, neuroprotection
Rhodiola (Salidroside)	Rhodiola rosea	↑ Monoamines, ↓ HPA overactivity, adaptogenic

8. Synergy in Phytotherapy: The Power of Herbal Combinations

In traditional healing systems such as Ayurveda, Traditional Chinese Medicine (TCM), Kampo (Japan), and Unani, the therapeutic application of phytochemicals rarely relies on single isolated compounds. Rather, these medical traditions emphasize multi-herb formulations designed to harness

synergistic interactions among plant constituents (Table 6). The principle of synergy—defined as a scenario where the cumulative therapeutic outcome of a combination of agents exceeds the sum of their individual effects—offers considerable promise in treating complex, multifactorial disorders like depression (Wagner, 2011).

These synergistic formulations are strategically developed to improve efficacy, minimize toxicity, and target diverse biological pathways implicated in mood regulation, including neurotransmitter balance, neuroinflammation, HPA axis modulation, and neurotrophic support.

8.1. Traditional Chinese Medicine (TCM) Formulas

In the TCM system, numerous classical formulations have demonstrated efficacy in alleviating depressive symptoms and have gained empirical support through modern pharmacological and clinical research. A prominent example is Xiao Yao San, also known as "Free and Easy Wanderer Powder," which comprises a synergistic blend of herbs including *Bupleurum chinense*, *Paeonia lactiflora*, *Angelica sinensis*, and *Glycyrrhiza uralensis*. This combination has been shown to regulate the HPA axis, enhance serotonin signaling, and restore emotional balance.

Mechanistically, Xiao Yao San promotes synaptic plasticity by enhancing BDNF expression and activating mitogen-activated protein kinase (MAPK) pathways. Additionally, it exerts potent anti-inflammatory effects by suppressing NF-κB signaling. Clinically, it is frequently used for depression associated with liver Qi stagnation and demonstrates positive outcomes in both mood and anxiety-related disorders.

Another widely used formula is Chai Hu Shu Gan San, which contains *Bupleurum*, *Citrus aurantium*, and other Qi-regulating botanicals. This formula enhances monoaminergic transmission, particularly serotonin and dopamine activity in the prefrontal cortex, leading to significant antidepressant-like effects in animal models (Wu et al., 2015).

8.2. Ayurvedic Polyherbal Preparations

In Ayurveda, multi-herb preparations like Saraswatarishta and Ashwagandharishta have been traditionally used to combat stress and depressive states. One particularly well-documented formulation is Brahmi Vati, which includes *Bacopa monnieri*, *Convolvulus pluricaulis*, and *Nardostachys jatamansi*. These herbs work synergistically to enhance mood and cognition, while simultaneously reducing cortisol levels and mitigating stress-induced neuronal damage. Clinical studies have demonstrated significant improvements in depressive scores following administration of Brahmi Vati, validating its adaptogenic and neuroprotective potential (Sharma et al., 2013).

Another commonly used combination involves *Ashwagandha*, *Shankhpushpi*, and *Jatamansi*, each contributing distinct pharmacological effects. Ashwagandha offers HPA axis regulation and BDNF activation; Shankhpushpi promotes

GABAergic modulation and antioxidant defense; while Jatamansi enhances serotonergic tone. Together, these botanicals provide a multifaceted approach to managing mild to moderate depression, particularly in patients presenting with stress-related symptoms.

8.3. Kampo Medicine Combinations (Japan)

Kampo medicine, Japan's traditional system derived from ancient Chinese practices, features formulations that are recognized and regulated by modern Japanese healthcare authorities. Yokukansan is one such Kampo formula, composed of herbs such as *Atractylodes lancea*, *Cnidium rhizome*, and *Angelica root*. This formula has shown efficacy in modulating glutamatergic excitotoxicity, a key mechanism implicated in depression. Yokukansan also enhances hippocampal serotonin levels and promotes BDNF expression, contributing to improved neuroplasticity and mood regulation (Ikarashi et al., 2010). Clinically, Yokukansan is used to manage neuropsychiatric symptoms in dementia and anxiety, and it shows growing promise in mood disorders as well.

8.4. Synergy with Conventional Antidepressants

Herbal-pharmaceutical combinations represent an important frontier in integrative psychiatry. Several phytochemicals have been found to potentiate the effects of conventional antidepressants or mitigate their side effects. For instance, co-administration of curcumin with fluoxetine enhances the antidepressant response by synergistically increasing BDNF expression and modulating monoaminergic activity. Piperine, an alkaloid from black pepper, improves the bioavailability of fluoxetine and reduces the required therapeutic dose, thereby potentially minimizing side effects. Similarly, resveratrol and ginsenosides enhance the neurotrophic response and behavioral outcomes when combined with standard antidepressants in chronic unpredictable mild stress (CUMS) models (Zhou et al., 2016).

Nevertheless, such combinations warrant caution due to possible herb-drug interactions, particularly with monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs). These interactions may either potentiate or inhibit drug metabolism, leading to altered therapeutic outcomes or adverse effects. Therefore, integration of herbal agents with pharmacotherapy must be based on sound pharmacokinetic and pharmacodynamic understanding (Sarris et al., 2011).

8.5. Mechanisms of Phytochemical Synergy

The synergistic efficacy observed in polyherbal and phytochemical-drug combinations arises from several underlying mechanisms. Multi-targeted actions are exemplified by combinations like ginseng and *Rhodiola rosea*, which modulate both the HPA axis and BDNF expression. Bioenhancement mechanisms also play a pivotal role; for instance, piperine increases the systemic availability of curcumin by inhibiting hepatic metabolism and enhancing intestinal absorption. In another example, quercetin is often

co-administered with lipophilic terpenes to optimize bioavailability and tissue penetration.

Moreover, some phytochemical combinations exhibit complementary receptor activity. Honokiol's action on GABA-A receptors, when paired with naringenin's enhancement of serotonin levels, exemplifies this type of synergistic modulation. Dual targeting of oxidative and inflammatory pathways is another cornerstone of phytochemical synergy. Resveratrol and silymarin, when combined, exert additive effects on inhibiting NF-κB and neutralizing reactive oxygen species (ROS), thereby offering robust protection against neuronal injury and mood dysregulation. Synergistic blends often amplify neuroprotective, anti-inflammatory, and antidepressant effects while reducing the required dosages of individual agents.

Table 6: Summary of Synergy in Phytotherapy for the management of Depression

Formulation / Combination	Key Components	Main Mechanisms
Xiao Yao San (TCM)	Bupleurum, Angelica, Licorice	↑ BDNF, ↓ HPA axis, anti-inflammatory
Brahmi Vati (Ayurveda)	Bacopa, Convolvulus, Nardostachys	↑ Mood, ↓ Cortisol, ↑ Cognition
Yokukansan (Kampo)	Atractylodes, Cnidium, Angelica	↑ 5-HT, ↑ BDNF, ↓ Glutamate
Curcumin + Fluoxetine	Curcumin + SSRI	↑ Efficacy, ↓ SSRI side effects
Ashwagandha + Shankhpushpi + Jatamansi	Adaptogens + Nootropics	Stress reduction, ↑ Monoamines, Neuroprotection

9. Preclinical Studies: Insights from Animal Models

Animal models of depression have played a foundational role in validating the efficacy of phytochemicals and uncovering their underlying mechanisms of action. These models mimic key features of human Major Depressive Disorder (MDD)—including behavioral despair, anhedonia, cognitive impairment, and neuroendocrine dysregulation—while providing reproducible systems for assessing biochemical and molecular responses to treatment. Below are the most widely used paradigms in depression research, each offering unique insights into the antidepressant properties of phytochemicals. The key findings from the preclinical model are presented in table 7.

9.1. Forced Swim Test (FST): The Forced Swim Test (FST), developed by Porsolt et al. (1977), remains a benchmark in antidepressant screening. In this assay, rodents placed in a cylinder of water display initial escape-directed movements followed by immobility, which is interpreted as behavioral despair. Phytochemicals such as apigenin, harmine, and linalool have demonstrated significant reductions in immobility time, correlating with increased BDNF expression and monoaminergic signaling (Porsolt et al., 1977; Kulkarni & Dhir, 2008).

<https://doi.org/10.53858/arocpb05020117>

9.2. Tail Suspension Test (TST): The Tail Suspension Test (TST), introduced by Steru et al. (1985), assesses despair-like behavior in mice by suspending them by the tail and measuring immobility duration. Curcumin, bacosides, and piperine have shown efficacy in reducing immobility, acting on serotonin and dopamine systems and reducing inflammatory mediators (Steru et al., 1985; Kulkarni et al., 2008).

9.3. Chronic Unpredictable Mild Stress (CUMS) Model
The CUMS model, as refined by Willner (1997), involves exposure to a variety of mild stressors over several weeks. It produces behaviors analogous to anhedonia and dysphoria, and models HPA axis dysregulation. Agents such as berberine and ginsenosides have reversed CUMS-induced changes in behavior, neurotrophic markers, and cytokine levels (Willner, 1997; Zhang et al., 2015).

9.4. Learned Helplessness and Social Defeat Models
The Learned Helplessness paradigm, pioneered by Seligman (1975), demonstrates that uncontrollable stress impairs later adaptive behavior. Phytochemicals like withanolides and harmine improve escape responses and normalize stress markers in this model (Seligman, 1975; Fortunato et al., 2009). The Social Defeat model, which exposes rodents to aggression-induced stress, is useful for studying chronic social stress. Compounds such as salidroside and naringenin show antidepressant-like effects by reversing social withdrawal and improving monoamine levels (Panossian & Wikman, 2010).

Table 7: Key Preclinical Findings

Compound /Class	Model Used	Key Outcomes
Curcumin	CUMS, FST	↑ BDNF, ↓ corticosterone, ↑ 5-HT & DA (Kulkarni et al., 2008)
Berberine	FST, CUMS	↑ monoamines, ↓ pro-inflammatory cytokines (Fan et al., 2017)
Resveratrol	Social defeat, LPS-induced	↑ neurogenesis, ↓ NF-κB, ↑ SIRT1 (Liu et al., 2014)
Ginsenosides	FST, CMS	↑ BDNF & CREB, improved mood behavior (Jiang et al., 2012)
Ashwagandha	Restraint stress	↓ cortisol, ↑ neuroplasticity (Bhattacharya et al., 2000)
Naringenin	FST, TST	↑ 5-HT & GABAergic tone (Golechha et al., 2012)
Honokiol	CUMS	↑ neurogenesis, ↓ inflammation (Li et al., 2015)

These studies collectively demonstrate that phytochemicals engage multiple pathways—neurotransmitter regulation, neuroinflammation suppression, and neurotrophic

enhancement—mirroring or even exceeding the effects of conventional antidepressants in some models.

10. Clinical Studies: Evidence in Humans

Although fewer in number compared to preclinical studies, clinical trials evaluating phytochemicals for depression are steadily increasing. These trials vary in design (open-label, randomized controlled trials [RCTs], crossover studies), populations (healthy, mild-to-moderate MDD), and outcome measures (e.g., BDI, HAM-D, MADRS). These findings underscore the utility of phytochemicals, either as monotherapy in mild cases or as adjunctive treatments to enhance efficacy and reduce the adverse effects of pharmacotherapy (Table 8).

10.2. Meta-Analyses and Systematic Reviews

Several meta-analyses provide compelling support for the efficacy of phytochemicals in the management of mood disorders. For instance, curcumin has demonstrated significant improvements in depressive symptoms, particularly among individuals with elevated inflammatory markers or comorbid metabolic conditions (Ng et al., 2017). Additionally, saffron, *Rhodiola rosea*, and *St. John's Wort* have shown consistent efficacy in mild-to-moderate depression with favorable tolerability and fewer adverse effects compared to conventional antidepressants (Sarris et al., 2011; Akhondzadeh et al., 2005).

Adaptogenic herbs such as *ashwagandha* have also demonstrated notable antidepressant and anxiolytic effects, improving resilience, lowering perceived stress, and modulating cortisol levels (Panossian & Wikman, 2010). However, the conclusions drawn from these analyses are often limited by small sample sizes, heterogeneity in herbal formulations and dosages, and the relatively short duration of most trials.

10.3. Safety, Tolerability, and Regulation

Phytochemicals are generally considered safe when administered in standard therapeutic doses. They tend to have lower toxicity and fewer side effects compared to many synthetic antidepressants (Sarris et al., 2011). Nevertheless, their potential to interact with conventional psychotropic medications is a concern. For example, *St. John's Wort* is known to induce cytochrome P450 enzymes, which may reduce the plasma levels of SSRIs, benzodiazepines, and oral contraceptives, and can increase the risk of serotonin syndrome when used concurrently with serotonergic drugs (Izzo & Ernst, 2009).

Standardization remains a major challenge, as the bioactive content of herbal products can vary significantly depending on the source, preparation method, and storage. Furthermore, most phytochemicals are marketed as dietary supplements rather than prescription drugs, allowing them to bypass

rigorous clinical and regulatory scrutiny in many countries (Walji et al., 2010).

Table 8: Highlighted Human Trials

Phytochemical	Trial Design	Population	Outcome
Curcumin	RCT, n=60	MDD	↓HAM-D scores, especially when combined with fluoxetine (Lopresti et al., 2015)
Ashwagandha	RCT, n=64	Adults with stress	↓ BDI and cortisol (Chandrasekhar et al., 2012)
Rhodiola	RCT, n=57	Mild to moderate MDD	Comparable to sertraline with fewer side effects (Darbinyan et al., 2007)
Lavender (Silexan)	RCT, n=221	GAD patients	Significant improvement in anxiety/depression scales (Woelk & Schlafke, 2010)
Bacopa	RCT, n=98	Healthy adults	Improved mood and cognition (Stough et al., 2008)
Resveratrol	Crossover, n=28	Smokers	↓depressive mood, CRP, and IL-6 (Bo et al., 2013)

11. Current Challenges in Phytochemical-Based Depression Therapy

Despite promising findings, several obstacles hinder the integration of phytochemical therapies into routine psychiatric care. The first is lack of standardization. Active constituents vary greatly due to plant species differences, cultivation methods, and preparation techniques. This variability complicates the interpretation of efficacy across studies and makes it difficult to develop universally accepted dosing guidelines (Heinrich et al., 2020).

Bioavailability limitations also affect clinical efficacy. Phytochemicals such as curcumin, quercetin, and resveratrol exhibit poor gastrointestinal absorption, rapid metabolism, and low CNS penetration. To overcome this, researchers are exploring novel delivery platforms, including nanoparticle-encapsulation, liposomal carriers, and the use of bioenhancers like piperine to improve systemic and brain bioavailability (Lopresti et al., 2015; Sharma et al., 2020).

Herb–drug interactions represent another key issue. Phytochemicals can inhibit or induce cytochrome P450 enzymes, potentially altering the metabolism of antidepressants and leading to subtherapeutic effects or adverse reactions (Izzo & Ernst, 2009). Clinical caution is especially warranted when combining phytochemicals with MAO inhibitors, SSRIs, or TCAs.

Moreover, many clinical trials investigating herbal antidepressants are underpowered, short-term, and lack consistent biomarkers or standardized scales, thereby limiting reproducibility and generalizability. Meta-analyses often highlight these issues, pointing to a need for higher methodological quality (Sarris et al., 2011).

From a regulatory standpoint, phytochemicals marketed as supplements are not subjected to the stringent safety, efficacy, and quality controls required of pharmaceuticals. This contributes to batch-to-batch variability and inconsistent therapeutic outcomes (Walji et al., 2010).

12. Future Perspectives and Research Directions

The future of phytochemical-based therapy for depression is promising and lies in personalized, mechanistically informed, and evidence-based approaches. Advances in genomics and microbiome science may allow clinicians to tailor phytotherapy based on genetic, epigenetic, or gut microbiota profiles (Clarke et al., 2013). Personalized phytomedicine could help identify individuals most likely to benefit from specific compounds.

Pharmaceutical innovations offer new ways to enhance bioavailability and therapeutic precision. Nanoparticle-based formulations, liposomes, and CNS-targeted delivery systems are under active investigation and may revolutionize the clinical utility of phytochemicals (Sharma et al., 2020).

The application of systems biology and multi-omics platforms can elucidate the broad pharmacodynamics of phytochemicals. Transcriptomics, proteomics, and metabolomics can help map the full spectrum of molecular targets and identify synergistic interactions in polyherbal formulations (Kibble et al., 2015).

Combining phytochemicals with standard treatments could improve outcomes in treatment-resistant depression. Rational polytherapy may enhance efficacy while minimizing adverse effects and allowing for dose reduction of synthetic drugs (Zhou et al., 2016).

Finally, well-powered, multicenter randomized controlled trials (RCTs) are essential. These should incorporate long-term follow-up, biomarker integration, and head-to-head comparisons with conventional antidepressants to solidify the role of phytochemicals in mainstream mental health care (Ng et al., 2017).

13. Conclusion

Depression is a complex and multifactorial disorder that demands multi-targeted therapeutic approaches.

Phytochemicals represent a valuable but underutilized armamentarium in mental health treatment. Derived from plants, these compounds modulate neurotransmission, reduce neuroinflammation, support neuroplasticity, and regulate stress responses—all of which are pathophysiological underpinnings of depression.

A growing body of evidence from animal models and human trials supports the antidepressant potential of several phytochemicals, including flavonoids (quercetin, apigenin), alkaloids (berberine, harmine), terpenes (curcumin, ginsenosides), lignans (honokiol), and adaptogens (ashwagandha, Rhodiola). Synergistic herbal combinations further enhance therapeutic outcomes. However, critical gaps remain in standardization, bioavailability, trial design, and clinical translation. Future research must prioritize pharmacokinetically optimized formulations, personalized treatment strategies, and rigorous efficacy assessments through large-scale, mechanistic clinical trials.

With thoughtful integration into existing treatment paradigms, phytochemicals hold the promise of augmenting depression management—particularly for patients seeking holistic, well-tolerated, and biologically diverse interventions.

Conflict of interests: The authors declare that they have no Conflict of interests.

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