Review Article

Healing the Depressed Brain Naturally: Neuroprotective Nutraceuticals and Phytochemical Interventions

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ABSTRACT

Major Depressive Disorder is one of the most prevalent psychiatric disorders worldwide and represents a major contributor to global disability, reduced productivity, and socioeconomic burden. Conventional antidepressants primarily target monoaminergic neurotransmitters such as serotonin and norepinephrine; however, their therapeutic limitations, delayed onset of action, adverse effects, and incomplete clinical response necessitate the exploration of alternative treatment strategies. Current evidence indicates that depression is a multifactorial disorder involving neurotransmitter imbalance, oxidative stress, neuroinflammation, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, impaired neuroplasticity, and altered neuronal signaling pathways. In recent years, increasing attention has been directed toward nutraceuticals and medicinal phytochemicals due to their multitargeted pharmacological properties and comparatively safer therapeutic profile. The present review highlights the neuroprotective and antidepressant potential of various medicinal plants and bioactive compounds through their interactions with molecular pathways associated with depression. Network-based and mechanistic approaches suggest that several phytochemicals modulate proteins and signaling systems involved in mood regulation, stress adaptation, inflammation, and neuronal survival. Medicinal plants such as Ephedra sinica, Curcuma longa, Panax ginseng, Ginkgo biloba, and Withania somnifera contain biologically active constituents including ephedrine, curcumin, ginsenosides, ginkgolides, crocin, hyperoside, salidroside, and withanolides, which exhibit antidepressant effects through antioxidant, anti-inflammatory, neuroprotective, adaptogenic, and neurotransmitter-modulating activities. These compounds regulate serotonergic, dopaminergic, noradrenergic, and neurotrophic signaling pathways while reducing oxidative damage and inflammatory responses associated with depressive disorders. Overall, nutraceuticals and phytochemicals represent promising complementary therapeutic approaches for the prevention and management of major depressive disorder. Their multitargeted mechanisms offer potential advantages over conventional single-target therapies. Nevertheless, further experimental validation, standardization, toxicity assessment, and large-scale clinical trials are required to establish their safety, efficacy, and clinical applicability in contemporary psychiatric practice.

Keywords: Major depressive disorder, nutraceuticals, phytochemicals, antidepressants, neuroprotection, oxidative stress, neuroinflammation, serotonin, medicinal plants, bioactive compounds.

INTRODUCTION

Depression is among the most prevalent mental health disorders worldwide, affecting more than 264 million people and contributing significantly to global disability and suicide-related mortality. Approximately 15% of suicide deaths are associated with depressive disorders, making depression a major public health concern. The condition arises through a complex interaction of genetic, biological, environmental, and psychosocial factors. Individuals with depression commonly experience persistent sadness, fatigue, hopelessness, low self-esteem, disturbed sleep, altered appetite, impaired concentration, and loss of interest in daily activities. Anxiety, suicidal ideation, and emotional instability may also accompany depressive episodes. These symptoms negatively influence occupational performance, academic achievement, interpersonal relationships, and overall quality of life, thereby increasing both social and economic burden on communities[1].

Several pharmacological approaches have been developed for the management of depression. Commonly prescribed antidepressants include monoamine oxidase inhibitors (MAOIs) such as isocarboxazid, moclobemide, and tranylcypromine; serotonin–norepinephrine reuptake inhibitors (SNRIs) including duloxetine, levomilnacipran, and venlafaxine; tricyclic antidepressants (TCAs) such as amitriptyline, desipramine, and imipramine; and selective serotonin reuptake inhibitors (SSRIs) including fluoxetine, escitalopram, and paroxetine. Although these medications are widely used, nearly half of patients show inadequate therapeutic response. Furthermore, antidepressants often require several weeks to exhibit clinical improvement and may produce adverse effects such as gastrointestinal disturbances, insomnia, dizziness, dry mouth, cardiovascular complications, sexual dysfunction, and weight changes. High treatment costs and poor tolerability frequently reduce patient compliance, thereby encouraging the exploration of safer and more affordable alternatives[2].

Since ancient times, humans have relied on phytotherapy and traditional systems of medicine, including Ayurveda and herbal medicine, to maintain physical and mental well-being. In many developing countries, medicinal plants continue to play a vital role in healthcare, particularly in rural regions with limited access to modern medical facilities. Historically, plants served as the primary source of therapeutic agents, and even today many pharmaceutical

compounds originate from natural products. Recent scientific investigations have identified several phytochemicals, including α-pinene, α-myrsinoic acid, and Mogroside V, as potential antidepressant agents. Compared with synthetic drugs, herbal medicines are often considered less toxic, more economical, and culturally acceptable[3].

The pathophysiology of depression involves multiple biological mechanisms. Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, oxidative stress, neuroinflammation, impaired neurogenesis, and altered neurotransmitter signaling involving serotonin (5-HT), dopamine (DA), and noradrenaline (NA) are strongly associated with depressive disorders. Reduced activity of receptors such as N-methyl-D-aspartate (NMDA) receptors may also contribute to disease progression. Many medicinal plants exert antidepressant effects through antioxidant, anti-inflammatory, neuroprotective, and neurotransmitter-modulating activities. Certain phytoconstituents additionally influence stress hormone regulation and neuronal plasticity, thereby supporting mental health improvement[4].

Considering the limitations of conventional antidepressants, nutraceuticals and phytotherapy represent promising complementary approaches for depression management. Traditional herbal remedies / nutraceuticals offer potential advantages such as accessibility, affordability, lower toxicity, and multi-target therapeutic effects. Continued scientific evaluation of nutraceuticals may lead to the discovery of novel antidepressant agents and provide safer adjunctive therapies for individuals suffering from depression. Thus, integrating traditional knowledge with modern pharmacological research could contribute significantly to future mental healthcare strategies[5].

TYPES OF MAJOR DEPRESSIVE DISORDERS

Depression is a complex mental health disorder that affects individuals in different ways. Various forms of depression exist, each characterized by distinct symptoms, duration, and triggering factors. Some types, such as major depressive disorder and bipolar disorder, are widely recognized, whereas others, including cyclothymic disorder and persistent depressive disorder, receive comparatively less attention. Certain depressive conditions are also associated with specific situations or seasons, such as postpartum depression following childbirth and seasonal affective disorder during winter months. Major depressive disorder is commonly referred to as clinical depression[5].

Major Depression

Major depression, also known as unipolar or clinical depression, is characterized by persistent sadness, loss of interest in pleasurable activities, and reduced motivation. Patients may experience psychomotor retardation, including slowed movements, delayed responses, and reduced activity levels. Depending on symptom severity, the disorder may be classified as mild, moderate, or severe. Subtypes of major depression include melancholic, psychotic, antenatal, and postnatal depression.

1. Melancholic Depression

Melancholic depression is a severe form of depressive illness marked by profound sadness and an inability to experience pleasure, even during positive events. Biological factors such as neurotransmitter dysfunction, excessive stress hormone activity, genetic predisposition, trauma, and chronic illness contribute significantly to its development. This condition is more common among middle-aged adults and individuals with a family history of mood disorders.

2. Persistent Depressive Disorder

Persistent depressive disorder, also known as dysthymia, is a chronic depressive condition lasting for at least two years in adults. Individuals commonly experience persistent low mood, hopelessness, fatigue, low self-esteem, sleep disturbances, appetite changes, and poor concentration. Although symptoms may appear less severe than major depression, their prolonged duration significantly affects occupational performance and interpersonal relationships. Risk factors include chronic stress, traumatic experiences, medical illnesses, and imbalances in neurotransmitters such as serotonin. Untreated cases may progress to major depression, anxiety disorders, substance abuse, and suicidal behavior.

3. Bipolar Disorder

Bipolar disorder is characterized by alternating episodes of depression and elevated mood states such as mania or hypomania. Its etiology involves genetic susceptibility, neurotransmitter imbalance involving dopamine and serotonin, hormonal changes, sleep disturbances, substance abuse, and stressful life experiences. Environmental stressors and emotional trauma may further worsen mood instability.

4. Seasonal Affective Disorder (SAD)

Seasonal affective disorder is a recurrent depressive condition associated with reduced sunlight exposure, particularly during winter months. Decreased sunlight lowers serotonin levels and disrupts melatonin secretion and circadian rhythm, resulting in sadness, fatigue, excessive sleepiness, and altered appetite. Vitamin D deficiency may also contribute to symptom development. SAD commonly affects young adults and is more prevalent among females and populations living in regions with prolonged winters.

5. Postnatal (Postpartum) Depression

Postnatal depression occurs after childbirth and may develop anytime within the first year postpartum. Symptoms include persistent sadness, anxiety, fatigue, disturbed sleep, reduced interest in daily activities, emotional withdrawal, and difficulty bonding with the new-born. Severe cases may involve suicidal thoughts or thoughts of harming the infant, requiring immediate medical attention. Rapid hormonal fluctuations, sleep deprivation, stress, previous psychiatric illness, and lack of social support are major contributing factors. Approximately one in seven women experiences postpartum depression.

6. Psychotic Depression

Psychotic depression is a severe subtype of depression accompanied by psychotic symptoms such as hallucinations or delusions. The condition is associated with dysregulation of neurotransmitters including serotonin and dopamine, hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, genetic predisposition, and structural brain abnormalities. Severe stress, trauma, substance abuse, and major medical illnesses may trigger or aggravate the condition.

7. Cyclothymic Disorder

Cyclothymic disorder is a chronic mood disorder characterized by recurrent fluctuations between mild depressive symptoms and hypomanic episodes that do not meet the diagnostic criteria for bipolar disorder. Mood instability may persist for several years and significantly interfere with daily functioning. The condition is associated with neurotransmitter imbalance, hereditary factors, chronic stress, and emotional trauma.

EPIDEMIOLOGY OF DEPRESSION

According to the World Health Organization, nearly 12% of the global population is affected by mental health disorders, with depression being one of the leading causes of disability worldwide (4 & 5). The prevalence of depression ranges between 3% and 10% globally, and women are more frequently affected than men. Approximately 10% of women experience depressive symptoms during or after pregnancy[6].

Individuals with chronic medical illnesses exhibit a higher prevalence of depression, ranging from 22% to 46%. Depression results from the interaction of multiple factors, including genetic predisposition, psychological vulnerability, stressful life events, environmental influences, infections, and biological abnormalities[7]. Emerging evidence highlights the role of epigenetics, where environmental factors interact with genetic mechanisms to influence disease susceptibility. Early-life adversity may increase long-term vulnerability to depressive disorders[8].

Several neurobiological alterations are associated with depression, including neurotransmitter imbalance, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, reduced brain-derived neurotrophic factor (BDNF) levels, oxidative stress, and glutamate-induced neuronal damage[9, 10]. These changes contribute to impaired neuroplasticity and emotional regulation, thereby influencing the progression and severity of depressive disorders and explained in Figure 1.

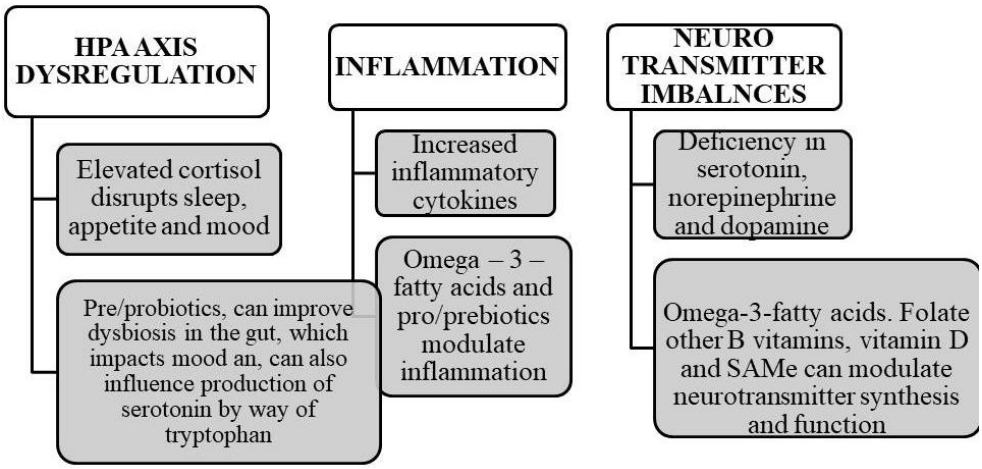


Figure 1: Actions of nutraceuticals on depression pathology

METHODOLOGY

The present review focuses on Major Depressive Disorder, its major subtypes and prevention or treatment strategies. Information was collected through a comprehensive review of published literature from reliable scientific sources, including Science Direct, Beyond Blue, and previously published research articles such as those from the International Journal of Pharmaceutical and Phytopharmacological Research. Relevant data regarding the definition, causes, symptoms, classifications, epidemiology, and theoretical concepts of depression were systematically gathered and organized. The collected information was critically analyzed, simplified, and arranged in a logical sequence to improve clarity and understanding for academic and research purposes.

Theories of Depression

Depression is a multifactorial disorder influenced by biological, psychological, environmental, and social factors. Various theories have been proposed to explain the origin and progression of depressive disorders. Modern understanding suggests that depression results from the interaction of neurochemical imbalance, stress, cognitive patterns, genetic predisposition, and environmental influences rather than a single causative factor.

Serotonin Theory of Depression

The serotonin hypothesis is one of the earliest biological theories of depression. It proposes that reduced serotonin activity in the brain contributes to depressive symptoms[11]. This reduction may result from decreased serotonin

synthesis, impaired neurotransmitter transport, or dysfunctional serotonin receptors[12]. Interest in serotonin increased during the 1960s with the development of selective serotonin reuptake inhibitors (SSRIs), which enhance serotonin availability. However, recent evidence indicates that depression is more complex than a simple serotonin deficiency[13]. Although serotonin plays an important role in mood regulation, current research suggests that depressive disorders involve multiple interacting neurobiological mechanisms[14].

Neurotrophic Hypothesis

The neurotrophic hypothesis states that chronic stress reduces the production of brain-derived neurotrophic factor (BDNF), a protein essential for neuronal growth, survival, and synaptic plasticity[15]. Reduced BDNF levels are associated with structural and functional changes in brain regions such as the hippocampus, which regulates memory and mood[16]. Decreased neurogenesis and neuronal atrophy may contribute to symptoms including sadness, cognitive impairment, and emotional instability[17]. Antidepressant therapies are believed to gradually improve BDNF levels and restore neuronal connectivity over time[18].

Inflammatory Theory

The inflammatory theory suggests that depression may arise from chronic inflammation within the body[19]. Stress, infection, or illness stimulates the release of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (20). These cytokines interfere with neurotransmitters including serotonin, dopamine, and norepinephrine, thereby affecting mood regulation.[21] Inflammation may also activate the hypothalamic–pituitary–adrenal (HPA) axis and reduce BDNF levels, leading to fatigue, anhedonia, low mood, and poor concentration.[22]

Hypothalamic–Pituitary–Adrenal (HPA) Axis Dysregulation

Dysregulation of the HPA axis is strongly associated with major depressive disorder.[23] Under normal conditions, the hypothalamus releases corticotropin-releasing hormone (CRH), stimulating the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which subsequently triggers cortisol release from the adrenal glands.[24] In depression, impaired negative feedback mechanisms lead to persistent elevation of cortisol levels. Excess cortisol adversely affects brain regions involved in mood regulation, particularly the hippocampus, and contributes to chronic stress responses and depressive symptoms.[25]

Psychological Theories of Depression

Psychological theories explain depression through emotional experiences, behavioral patterns, cognition, and interpersonal relationships.[26] These theories highlight how learning experiences, thought processes, unresolved conflicts, and social interactions contribute to depressive disorders.[27]

Behaviourist Theory

The behaviourist theory proposes that depression develops due to reduced positive reinforcement from the environment. According to this theory, stressful experiences, social withdrawal, and decreased participation in enjoyable activities reduce opportunities for reward and satisfaction. As pleasurable experiences decline, individuals become increasingly inactive and isolated; creating a cycle that reinforces depressive behavior.[28] The theory is particularly useful in explaining depression following loss, stress, or major life changes.

Psychodynamic Theory

The psychodynamic theory explains depression as the result of unresolved unconscious conflicts and early childhood experiences. Suppressed emotions, feelings of loss, guilt, rejection, or anger may become internalized, leading to self-criticism and low self-worth. According to Sigmund Freud, depression may occur when grief and emotional pain are directed inward toward oneself. [29] Early emotional neglect and insecure relationships may increase vulnerability to depressive disorders later in life.

Learned Helplessness Theory

The learned helplessness theory, proposed by Martin Seligman, suggests that repeated exposure to uncontrollable negative events causes individuals to believe they are powerless to change their circumstances.[30] Over time; this belief reduces motivation, problem-solving ability, and emotional resilience. Persistent feelings of helplessness and hopelessness contribute significantly to depressive symptoms.[31]

Attachment Theory

The attachment theory, developed by John Bowlby, emphasizes the importance of early emotional bonds between children and caregivers.[32] Secure attachments formed during childhood promote emotional stability and healthy coping mechanisms. In contrast, inconsistent care, neglect, or emotional rejection may lead to insecure attachment patterns, increasing vulnerability to depression in adulthood. Individuals with insecure attachment styles often experience difficulties in relationships, stress management, and emotional regulation.[33]

Current evidence suggests that depression cannot be explained by a single theory alone. Instead, depressive disorders arise through the interaction of neurochemical abnormalities, chronic stress, inflammation, psychological factors, genetic predisposition, and environmental influences. Understanding the various biological and psychological theories of depression provides a comprehensive framework for developing effective therapeutic approaches and improving mental health management strategies and overview of depression depicted in Table 1.

Table 1: Symptoms, Prevention and Treatment of Depression

Category	Key Features	Clinical Importance
Symptoms of Depression	Sadness, irritability, emptiness, poor concentration, guilt, hopelessness, suicidal thoughts, sleep disturbances, appetite changes, fatigue	Early identification helps in timely management
Patterns of Depression	Single depressive episode, recurrent depressive episodes, depression associated with mood swings	Determines treatment approach and prognosis
Contributing Factors	Stressful life events, alcohol use, lack of exercise, poor physical health	Lifestyle modification reduces risk
Preventive Strategies	Regular exercise, healthy diet, reduced alcohol intake, social support, stress management	Improves emotional resilience and mental wellness
Psychological Therapies	Cognitive behavioural therapy, interpersonal psychotherapy, problem-solving therapy	First-line treatment in mild-to-moderate depression
Pharmacological Treatment	Antidepressants such as fluoxetine	Used in moderate-to-severe depression
Suicide Prevention	Counselling, emotional support, healthcare consultation, open communication	Reduces risk of self-harm and improves recovery

NUTRACEUTICALS AND PHYTOCHEMICALS IN DEPRESSION MANAGEMENT

Nutraceuticals: Definition and Therapeutic Importance

Nutraceuticals are food-derived products that provide both nutritional and medicinal benefits. The term “nutraceutical” was introduced in 1989 by Stephen DeFelice by combining the words “nutrition” and “pharmaceutical.” Unlike conventional dietary supplements that mainly compensate for nutrient deficiencies, nutraceuticals possess therapeutic properties that may help prevent, manage, or reduce the progression of diseases. [34, 35]

Nutraceuticals are obtained from natural food sources and may be present as functional foods, fortified products, isolated nutrients, or purified bioactive compounds. Recent advances in nanotechnology, including nanoemulsions and lipid-based delivery systems, have improved their bioavailability and therapeutic efficacy. [36] Because these compounds originate from natural dietary sources, they are generally considered safer and more acceptable for long-term use compared to synthetic medications.

In depressive disorders, nutraceuticals have gained considerable attention due to their antioxidant, anti-inflammatory, neuroprotective, and neurotransmitter-modulating properties. They may improve brain function, regulate stress responses, enhance neuroplasticity, and support neurotransmitter synthesis. [37] Nutraceuticals are therefore increasingly explored as adjunctive or alternative therapies for depression, particularly in patients who show poor response or intolerance to conventional antidepressants.

Significance of Phytochemicals in Depression

Phytochemicals are naturally occurring chemical compounds present in medicinal plants and herbs. [38] Several phytochemicals exhibit antidepressant potential by modulating neurotransmitters such as serotonin, dopamine, and norepinephrine, while also reducing oxidative stress and inflammation associated with depressive disorders. [39, 40] Compared with synthetic antidepressants, plant-derived compounds may offer fewer adverse effects and better patient compliance.

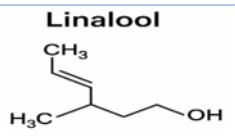
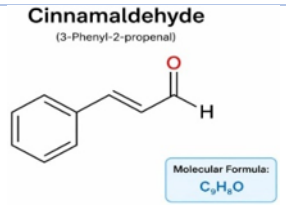
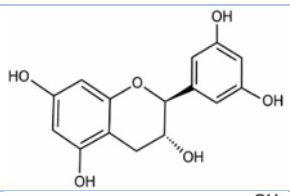
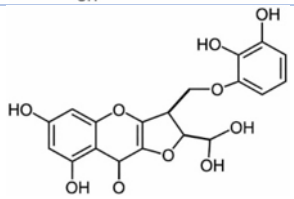
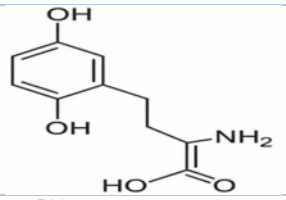
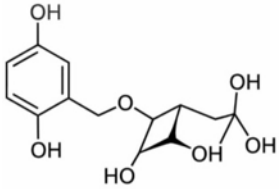
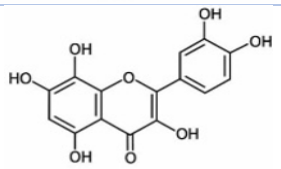
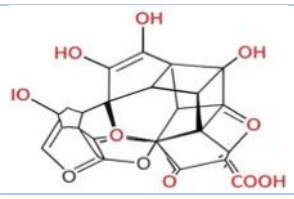
Medicinal plants including saffron, turmeric, lavender, and St. John's Wort etc., have shown promising therapeutic effects in depression management cited in Table 2.

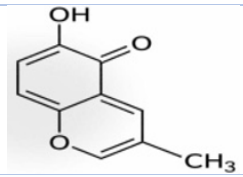
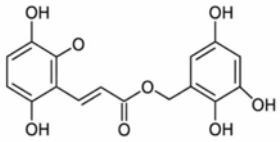
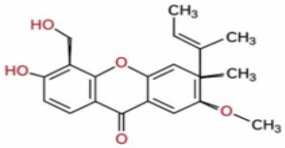
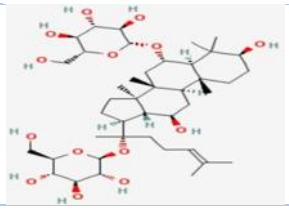
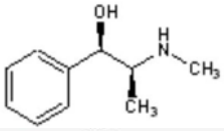
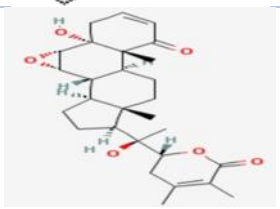
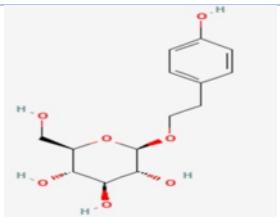
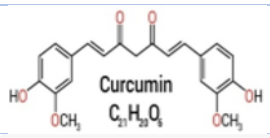
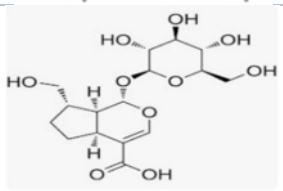
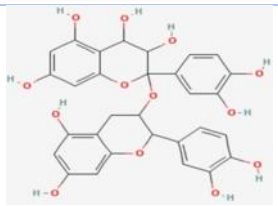
Role of Nutraceuticals in Depression Disorders

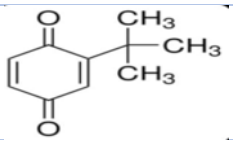
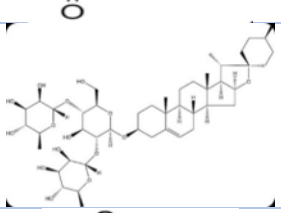
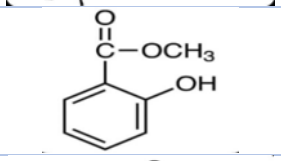
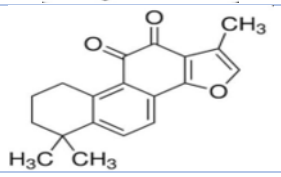
Depression is associated with multiple pathological mechanisms, including neurotransmitter imbalance, oxidative stress, neuroinflammation, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, and reduced neurotrophic support. Nutraceuticals and phytochemicals target these mechanisms through multiple pathways simultaneously. [41] Their antioxidant and anti-inflammatory effects protect neuronal cells, while their influence on neurotransmitters and neurotrophic factors improves mood, cognition, and emotional stability.

Several studies suggest that nutraceuticals may enhance the effectiveness of conventional antidepressant therapy and reduce associated adverse effects. [42, 43] Due to their affordability, accessibility, and relatively lower toxicity, nutraceuticals represent a promising complementary strategy for the long-term management of depressive disorders. [44] Continued scientific investigations into plant-derived compounds may further contribute to the development of safer and more effective therapeutic options for mental health disorders. [45]

Table 2:

Phytochemical name	Chemical structure	Dose	Route of administration	Adverse drug reactions
Crocin *(Crocus sativus)*		Paediatrics: 10-20 mg /day Adult :30-60 mg /day Geriatrics: 15-30 mg /day	Oral (capsule, tablet, extract)	Nausea, dizziness, hypotension, bleeding (rare)
Linalool *(Cinnamomum tamala)*		Adult: 50-200 mg/day (if oral) Geriatrics: low doses preferred	Inhalation, topical, oral	Sedation dizziness, skin irritation
Cinnamaldehyde *(Cinnamomum zeylanicum)*		Adult:100-500 mg /day(as extract)	Oral, topical (oil diluted)	GI irritation, hepato toxicity, (high dose), allergy
Epicatechin *(Theobroma cocoa)*		Adult and geriatrics:50-200 mg/day	Oral (tea, cocoa, supplements)	GI upset, headache
Hyperoside *(Apocynum venetum)*		Adult :500-1000 mg/day Pediatrics : 5-10 mg/kg/day Geriatics :400-800 mg/day	Oral	Gastro Intestinal Upset (mild), sedation, hypotension
Mimosine *(Mimosa pudica)*		Adults: 300-600 mg/day Geriatrics:250-500 mg/day	Oral	Nausea, vomiting , hair loss, dizziness
Gastrodinn *(Gastrodiaelata volume)*		Adults :300-600 mg/day Pediatrics:5-10 mg/kg/day Geriatics:250-500 mg/day	Oral, IV	Mild GI upset, headache, dizziness, allergic reactions (rare)
Quercetin *(Cuscuta chinensis)*		Adult :500-1000 mg/day Pediatrics:5-10 mg/kg/day Geriatrics :400-800 mg/day	Oral	Headache , GI upset, tingling, kidney stress (high dose)
Ginkgolide B *(Ginkgolide biloba)*		Adult:120-240 mg/day Pediatrics:60-120 mg/day Geriatrics:120-140 mg/day	Oral	Headache, GI upset, dizziness, bleeding risk

Scopoletin *(Convolvulus pluricaulis)*		Adult :500-1000 mg/day Pediatrics:5-10 mg/kg/day Geriatics:400-800 mg/day	Oral	Mild sedation, GI discomfort, dry mouth, fatigue
Rosmarinic acid *(Echium amoenum)*		Adult :500-1000 mg/day Pediatrics:5-10 mg/kg/day Geriatrics:400-800 mg/day	Oral	GI upset, dizziness, sedation, allergic reactions
Alpha mangostin *(Garcinia mangostana)*		Adult500-1000 mg/day Pediatrics:5-10 mg/kg/day Geriatrics:400-800 mg/day	Oral	GI discomfort, headache, fatigue, allergic reactions
Ginsenosides *(Panax ginseng)*		Adult:200-900 mg/day Geriatrics:100 -200 mg/day	Oral (capsule, tablet, powder, decoction) Topical creams	Insomnia, headache, alternate blood pressure
Ephedrine *(Ephedra sinica)*		Adult :25-50mg 2 to 3 times/day Geriatrics 12.5 -25 mg/day	Oral (tablet, decoction) Rarely parenteral	Hypertension, tremors, nausea, sweating, urinary retention
Withanolides *(Withania somnifera)*		Adult:300-600 mg/day Pediatrics:50-100 mg/day Geriatrics:250-300 mg /day	Oral	Mild GI upset, drowsiness, headache, possible thyroid stimulation
Salidroside *(Rhodiola rosea)*		Adult:200-600 mg/day Geriatrics:100-200 mg/day	Oral	Insomnia, irritability, dry mouth, dizziness, and headache.
Curcumin longa (Curcumin)		Adult : 4-5g/day	Oral, topical	GI upset, Headache, Bleeding risk
Nardostachys jatamansi (Jatamansi)		Adult: 300-500mg/day	Oral, oil for external use	Sedation, Hypotension, Allergic reactions
Pinus pinaster (Procyanidins)		Adult:50 -200mg/day	Oral	Dizziness, GI upset, headache

Rapanea ferruginea (Myrsinoic acid)		Pediatrics: 5-10mg/kg/day Adult dose:100-300mg/day Geriatrics:50-150mg/day	Oral , Topical	GI irritation, Nausea, Allergy
Bacopa monnieri (Brahmi)		Pediatrics:5-10mg/kg/day Adult:300-600 Mg/day Geriatrics:150-300mg/day	Oral	Nausea , dry mouth, fatigue
Viola odorata (Violin , methyl salicylate)		Pediatrics:2.5-5ml syrup Adult:100-200 Mg extract Geriatrics:5ml syrup	Oral	GI irritation, Allergy , Vomiting
Salvia miltiorrhiza (Tanshinones , salvianolic acid B)		Pediatrics:2-5mg/kg/day Adult:200-400mg/day 5-10 gm crude Geriatrics:100-200mg/day	Oral , injectable	Bleeding risk, dizziness, GI upset

Nutraceuticals and Herbal Compounds in Major Depressive Disorder

Natural products and nutraceuticals have gained increasing attention in the management of Major Depressive Disorder due to their antioxidant, anti-inflammatory, neuroprotective, and neurotransmitter-modulating activities. [46, 47] Many medicinal plants and phytochemicals influence multiple biological pathways involved in depression, including serotonin, dopamine, norepinephrine, brain-derived neurotrophic factor (BDNF), oxidative stress, neuroinflammation, and hypothalamic–pituitary–adrenal (HPA) axis dysregulation and few dietary nutraceuticals illuminated in Table 3[48,49]. Compared with conventional antidepressants, several herbal compounds show fewer adverse effects and may serve as complementary or adjunctive therapies. [50, 51]

Crocin

Saffron obtained from *Crocus sativus* contains crocin, a bioactive carotenoid responsible for its antidepressant properties. [52] Crocin exhibits neuroprotective, antioxidant, anti-inflammatory, and cognitive-enhancing effects. Its antidepressant activity is associated with inhibition of serotonin, dopamine, and norepinephrine reuptake, modulation of monoamine oxidase activity, NMDA receptor antagonism, and increased expression of BDNF, VEGF, and p-CREB in the hippocampus[53, 54]. Clinical studies indicate that saffron supplementation significantly improves depressive symptoms and may produce effects comparable to fluoxetine. [55]

Linalool

Linalool is a naturally occurring terpene alcohol present in lavender, bergamot, and citrus oils. [56] It exerts anxiolytic and antidepressant effects through modulation of GABAergic neurotransmission and interactions with serotonergic and noradrenergic pathways.[57] Aromatherapy with linalool-rich essential oils has demonstrated beneficial effects in reducing anxiety, stress, and depressive symptoms. Linalool also enhances parasympathetic activity, promotes relaxation, improves sleep quality, and exhibits neuroprotective properties. [58]

Cinnamaldehyde

Cinnamon contains cinnamaldehyde, an active phytochemical with anti-inflammatory and antidepressant potential. [59] Experimental studies show that cinnamaldehyde suppresses inflammatory mediators including TNF-α, IL-1β, IL-18, and COX-2 through inhibition of NF-κB and NLRP3 inflammasome pathways. [60] It also regulates BDNF-associated signaling pathways and reduces neuroinflammation in the hippocampus and prefrontal cortex. Animal studies demonstrate significant improvement in depressive-like behavior following cinnamaldehyde administration. [61]

Epicatechin from Cocoa

Cocoa contains epicatechin, catechins, flavonoids, and methylxanthines such as theobromine and caffeine. [62] These compounds improve mood by increasing serotonin, dopamine, and norepinephrine levels, reducing oxidative stress, enhancing cerebral blood flow, increasing BDNF levels, and modulating gut–brain communication. [63] Cocoa flavonoids also exhibit anti-inflammatory and neuroprotective effects that contribute to improved cognitive function and emotional stability. [64]

Apocynum venetum

Apocynum venetum contains flavonoids including hyperoside, quercetin, and kaempferol. [65] Hyperoside exhibits antidepressant effects through monoamine oxidase inhibition, antioxidant activity, HPA axis regulation, anti-inflammatory effects, and increased BDNF expression. [66] It also modulates intracellular signaling pathways such as

PI3K/Akt and MAPK, thereby protecting neurons from oxidative damage and stress-induced apoptosis. [67]

Mimosa pudica

Mimosa pudica possesses alkaloids, flavonoids, terpenoids, and tannins with neuroprotective properties.[68] Ethyl acetate extracts of the plant demonstrate antidepressant-like activity by increasing dopamine and norepinephrine levels without causing excessive locomotor stimulation. Animal studies also reveal anxiolytic and cognitive-enhancing effects, suggesting its potential role as an adjunctive treatment for depressive disorders. [69]

Gastrodia elata

Gastrodia elata, commonly known as Tianma, contains gastrodin and other neuroactive compounds. [70] These constituents exert antioxidant, anti-inflammatory, and neuroprotective actions that reduce depressive-like behaviors. Gastrodin improves neuronal survival, decreases oxidative damage, and supports cognitive function through modulation of neuroinflammatory pathways. [71]

Cuscuta chinensis

Cuscuta chinensis exhibits antidepressant potential through antioxidant, anti-inflammatory, and neurotransmitter-modulating activities. [72] The plant regulates serotonin and norepinephrine signaling, suppresses NF-κB-mediated neuroinflammation, and enhances gut–brain axis function. Flavonoids and alkaloids present in the plant contribute significantly to its mood-enhancing effects. [73]

Ginkgolide B

Ginkgo biloba extract EGb 761 contains flavonoids and terpene lactones such as ginkgolides and bilobalide. [74] These compounds exhibit antidepressant effects by inhibiting norepinephrine transporters, increasing dopamine levels in the prefrontal cortex, reducing oxidative stress, regulating the HPA axis, increasing BDNF levels, and suppressing neuroinflammation. EGb 761 additionally improves cerebral circulation and protects neuronal integrity. [75, 76]

Convolvulus pluricaulis

Convolvulus pluricaulis possesses alkaloids, flavonoids, and scopoletin that contribute to antidepressant activity. The herb modulates serotonin, dopamine, and GABAergic pathways, reduces inflammatory cytokines, and enhances antioxidant defense mechanisms. [77] It also improves brain metabolism and stress adaptation. [78]

Echium amoenum

Echium amoenum demonstrates antidepressant and anxiolytic effects through regulation of serotonin and dopamine neurotransmission, reduction of inflammatory mediators, antioxidant protection, and HPA axis modulation. Bioactive constituents such as rosmarinic acid, flavonoids, anthocyanins, and gamma-linolenic acid contribute to its therapeutic activity[79, 80].

Garcinia mangostana

Mangosteen contains xanthones including alpha-mangostin with strong antioxidant and anti-inflammatory properties. [81] These compounds reduce oxidative stress, inhibit inflammatory cytokines, regulate serotonin pathways, and protect neurons from degeneration. Mangosteen may therefore support mood stabilization and cognitive health.[82]

Ginsenosides

Panax ginseng contains ginsenosides that improve depressive symptoms through modulation of serotonin, dopamine, and norepinephrine pathways. [83] Ginseng also regulates cortisol production, reduces neuroinflammation, enhances antioxidant defenses, and increases BDNF expression. [84] Its adaptogenic activity improves stress tolerance and mental performance (85).

Ephedrine

Ephedra sinica contains ephedrine and pseudoephedrine, which stimulate central nervous system activity by increasing norepinephrine and dopamine release.[86] Although these compounds may transiently improve alertness and mood; their adverse cardiovascular and neurological effects limit their therapeutic use in depression. [87]

Withanolides

Ashwagandha contains withanolides that exert antidepressant effects through HPA axis regulation, cortisol reduction, enhancement of GABAergic activity, and modulation of serotonin and dopamine pathways. [88, 89] Ashwagandha also increases BDNF expression, reduces neuroinflammation, improves sleep, and protects neurons from oxidative damage. [90]

Salidroside

Rhodiola rosea contains salidroside and rosavins that regulate stress responses by modulating the HPA axis and lowering cortisol levels. [91] Rhodiola improves mood through enhancement of serotonin, dopamine, and norepinephrine activity while simultaneously reducing oxidative stress and inflammation. [92] It additionally improves cognitive function, energy production, and mental resilience. [93]

Curcumin

Turmeric contains curcumin, a polyphenolic compound with strong antidepressant activity. [94] Curcumin increases serotonin, dopamine, and norepinephrine availability, suppresses neuroinflammatory pathways, reduces oxidative stress, enhances BDNF expression, regulates glutamate toxicity, and stabilizes the HPA axis. [95] These combined actions contribute to improved emotional and cognitive function. [96]

Nardostachys jatamansi

Nardostachys jatamansi contains jatamansone and other sesquiterpenes with antidepressant and anxiolytic properties. [97] The herb modulates monoamine

neurotransmitters, enhances GABA activity, reduces cortisol levels, suppresses inflammatory cytokines, and increases antioxidant enzyme activity. It additionally supports neuronal growth and protects against glutamate-induced neurotoxicity. [98]

Pinus pinaster

Pinus pinaster produces Pycnogenol, a procyanidin-rich antioxidant extract. [99] Pycnogenol reduces oxidative stress, improves cerebral blood flow, supports neurotransmitter balance, decreases inflammation, and lowers stress-induced cortisol production. These properties contribute to improved mood, cognition, and fatigue reduction.[100]

Myrsinoic Acid

Myrsine coriacea contains myrsinoic acids A and B with demonstrated antidepressant-like activity in experimental models.[101] These compounds reduce immobility behavior in forced swim tests and exert antioxidant effects in the hippocampus and prefrontal cortex, thereby improving depressive-like symptoms.[102]

Brahmi

Brahmi contains bacosides and bacopasaponins that regulate serotonin, dopamine, GABA, and cortisol levels (103). Brahmi exhibits antidepressant, anxiolytic, antioxidant, and neuroprotective effects while enhancing cognition, memory, and stress tolerance (104). Clinical observations during the COVID-19 pandemic also suggest beneficial effects on depression, anxiety, and stress reduction.[105]

Viola odorata

Viola odorata possesses flavonoids with antidepressant activity mediated primarily through serotonergic pathways.[106] Experimental studies demonstrate antidepressant-like effects in forced swim and tail suspension tests, while clinical trials report significant reductions in depressive symptoms and insomnia following administration of *Viola odorata* syrup.[107]

Salvia miltiorrhiza

Salvia miltiorrhiza contains tanshinones and salvianolic acids with antioxidant, anti-inflammatory, vasodilatory, and neuroprotective activities.[108] These compounds improve cerebral blood flow, protect neurons against ischemic damage, reduce oxidative stress, and suppress inflammatory mediators implicated in depression and neurodegenerative disorders. [109,110]

Toxicity and Safety of Medicinal Plants

Although medicinal plants and nutraceuticals are generally considered safer than synthetic drugs, their use still requires caution.[111] Certain herbal products may accumulate toxic heavy metals such as lead and cadmium due to environmental contamination. Improper storage conditions can also result in fungal contamination and toxin production.[112] Furthermore; many herbal preparations lack standardized manufacturing practices, quality control, and certification.[113] Excessive or unsupervised use may produce hepatic, renal, cardiovascular, or neurological toxicity. Therefore, scientific validation, proper dosage regulation, toxicity evaluation, and standardization are essential for the safe therapeutic application of herbal medicines in depression management.[114]

Table: 3 Dietary Nutraceuticals in Controlling Depression

Nutraceutical	Dosage Range	Primary Use	Mechanism of Action	Major Benefits	Important Precautions / Side Effects
Omega-3 Fatty Acids	1–2 g/day	Adjunctive and Monotherapy	Anti-inflammatory action; improves neuronal membrane fluidity and neurotransmission	Improves mood, cognition, emotional stability	High doses may increase bleeding risk in patients using anticoagulants
S-Adenosyl Methionine	400–1600 mg/day	Adjunctive and Monotherapy	Acts as methyl donor; modulates serotonin and dopamine neurotransmitters	Enhances mood and emotional balance	May cause anxiety, insomnia, or gastrointestinal upset in sensitive individuals
L-Methylfolate	7.5–15 mg/day	Adjunctive	Increases monoamine neurotransmitter synthesis	Helpful in folate-deficient depression and antidepressant resistance	Excess intake may mask vitamin B12 deficiency
Vitamin D3	1500–4000 IU/day	Adjunctive	Supports serotonin synthesis via activation of TPH2 gene	Improves mood and immune health	Excessive use may cause hypercalcemia
Zinc Supplementation	25 mg/day	Adjunctive	Enhances neurotransmission and reduces oxidative stress	Supports cognitive and emotional functions	Excessive intake may produce nausea and copper deficiency
Probiotics	1–10 billion CFU/day	Adjunctive	Modulates gut–brain axis and intestinal microbiota	Improves stress response and emotional well-being	Mild bloating or gastrointestinal discomfort may occur
St. John's Wort	300 mg three times daily	Monotherapy	Inhibits monoamine reuptake	Effective in mild-to-moderate depression	Significant drug interactions due to CYP450 enzyme induction
5-Hydroxytryptophan	50–300 mg/day	Monotherapy	Precursor of serotonin synthesis	May improve sleep and mood	Risk of serotonin syndrome when combined with antidepressants

DISCUSSION

Major depressive disorder (MDD) is a multifactorial psychiatric illness involving disturbances in neurotransmitter signaling, neuroinflammation, oxidative stress, impaired neuroplasticity, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, and altered neuronal survival. Conventional antidepressants such as selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs) mainly target monoaminergic pathways; however, their delayed onset of action, adverse effects, poor patient compliance, and incomplete therapeutic response highlight the need for safer and more comprehensive treatment approaches. In recent years, nutraceuticals and phytochemicals have emerged as promising complementary strategies for the prevention and management of depression due to their multitargeted pharmacological activities.

The present review demonstrates that several plant-derived nutraceuticals influence multiple biological pathways associated with depression simultaneously rather than acting on a single target. This multi-mechanistic approach is particularly important because the pathogenesis of depression involves interconnected neurochemical, inflammatory, endocrine, and oxidative pathways. Nutraceuticals possess antioxidant, anti-inflammatory, neuroprotective, adaptogenic, and neurotransmitter-modulating properties that may contribute to improved emotional stability, cognitive performance, and stress resilience.

Among the most extensively studied phytochemicals, crocin from Saffron showed significant antidepressant potential through modulation of serotonin, dopamine, and norepinephrine pathways, enhancement of BDNF signaling, and suppression of oxidative stress. Clinical studies comparing saffron with fluoxetine suggest that crocin-containing preparations may provide clinically meaningful improvement in depressive symptoms with comparatively fewer adverse effects. Similarly, curcumin from Turmeric demonstrated broad-spectrum neuroprotective effects by reducing inflammatory cytokines, regulating glutamate toxicity, enhancing BDNF expression, and improving neurotransmitter availability. The ability of curcumin to influence both neuroinflammatory and neuroplastic pathways make it particularly valuable in stress-related and chronic depressive disorders.

Adaptogenic herbs such as Ashwagandha and *Rhodiola rosea* play a significant role in stress-associated depression through regulation of the HPA axis and reduction of cortisol levels. Chronic stress is strongly associated with neuronal damage, emotional instability, sleep disturbances, and impaired cognitive function. Withanolides from Ashwagandha and salidroside from Rhodiola improve stress adaptation, enhance GABAergic signaling, and promote neuronal survival, thereby contributing to emotional resilience and improved mental health outcomes.

The findings also emphasize the importance of antioxidant-rich nutraceuticals in depression management. Oxidative stress contributes substantially to neuronal dysfunction and reduced neuroplasticity in MDD. Compounds such as epicatechin from Cocoa, ginkgolides from *Ginkgo biloba*, hyperoside from *Apocynum venetum*, and procyanidins from *Pinus pinaster* significantly reduce oxidative damage while improving cerebral circulation and mitochondrial function. These effects help preserve neuronal integrity and support cognitive function, memory, and emotional regulation.

Several phytochemicals additionally demonstrated strong anti-inflammatory activities. Neuroinflammation has become a central focus in contemporary depression research because elevated cytokines such as TNF-α, IL-1β, and IL-6 are frequently observed in depressed patients. Nutraceuticals including cinnamaldehyde, curcumin, Echium amoenum extracts, and salvianolic acids from Salvia miltiorrhiza suppress inflammatory mediators and inhibit pathways such as NF-κB and NLRP3 inflammasome activation. Through reduction of inflammatory signaling, these compounds may protect neurons from chronic inflammatory injury and improve mood-related brain function.

Another important observation is the growing evidence supporting gut–brain axis modulation in depression prevention and treatment. Certain nutraceuticals, particularly cocoa flavonoids and *Cuscuta chinensis* constituents, may promote beneficial intestinal microbiota and reduce systemic inflammation. Since gut microbiota influence neurotransmitter production, immune regulation, and stress responses, targeting the gut–brain axis represents an important contemporary strategy in depression management.

In the current era, nutraceuticals are gaining global importance because of increasing mental health burden, lifestyle-related stress, rising treatment costs, and concerns regarding long-term adverse effects of synthetic antidepressants. Plant-derived compounds offer several practical advantages, including affordability, accessibility, cultural acceptance, and lower toxicity when used appropriately. Furthermore, many nutraceuticals can be integrated into daily dietary practices as preventive mental health strategies. Functional foods rich in omega-3 fatty acids, polyphenols, flavonoids, vitamins, probiotics, and adaptogenic herbs may support emotional stability and reduce the risk of chronic stress-related disorders.

Despite these promising findings, several limitations remain. Most evidence regarding phytochemicals in depression originates from preclinical studies and animal models, whereas large-scale randomized clinical trials in humans remain limited. Variability in extraction methods, dosage forms, bioavailability, and phytochemical standardization also creates challenges in comparing therapeutic outcomes across studies. Additionally, certain medicinal plants may interact with conventional antidepressants or produce adverse effects at higher doses. Therefore, standardization,

pharmacovigilance, toxicity assessment, and evidence-based dosage guidelines are essential before widespread clinical application can be recommended.

Overall, the present review highlights that nutraceuticals and phytochemicals possess significant therapeutic potential in both the prevention and management of major depressive disorder. Their multitargeted actions on neurotransmitters, oxidative stress, neuroinflammation, neuroplasticity, and endocrine regulation provide a comprehensive approach that aligns with the complex pathophysiology of depression. In the contemporary era of integrative medicine, nutraceuticals may serve not only as adjunctive therapies but also as preventive tools for improving mental health, emotional resilience, and quality of life. Future research should focus on clinical validation, mechanistic studies, formulation development, and long-term safety evaluation to establish nutraceuticals as scientifically accepted therapeutic options in psychiatric healthcare.

CONCLUSION

Major depressive disorder is now recognized as a complex and multifactorial psychiatric condition involving neurotransmitter imbalance, neuroinflammation, oxidative stress, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, and impaired neuroplasticity. Although conventional antidepressants remain the primary therapeutic option, their delayed onset of action, incomplete clinical response, adverse effects, and poor patient compliance continue to limit their overall effectiveness. These limitations have encouraged growing interest in alternative and complementary therapeutic strategies. Nutraceuticals and phytochemicals have emerged as promising candidates in the prevention and management of depression due to their multitargeted pharmacological actions. Bioactive compounds such as crocin, epicatechin, hyperoside, curcumin, ginsenosides, withanolides, and salidroside demonstrate antioxidant, anti-inflammatory, neuroprotective, adaptogenic, and neurotransmitter-modulating activities. These compounds influence several biological pathways associated with depression, including serotonin, dopamine, norepinephrine, BDNF signaling, oxidative stress reduction, and regulation of stress-related hormonal responses. Unlike conventional antidepressants that primarily target single neurotransmitter systems, nutraceuticals exert broader therapeutic effects by simultaneously acting on interconnected neurobiological mechanisms. The integration of traditional herbal knowledge with modern neuropharmacological research provides new opportunities for the development of safer, affordable, and accessible therapeutic interventions for depressive disorders. Nutraceuticals may serve not only as adjunctive therapies alongside standard antidepressants but also as preventive approaches for stress-related mental health conditions in contemporary society.

However, despite encouraging preclinical and clinical findings, further scientific validation remains essential. Standardization of herbal preparations, optimization of dosage regimens, evaluation of long-term safety, and large-scale randomized clinical trials are necessary before these compounds can be fully integrated into evidence-based psychiatric practice. Future research focusing on mechanistic pathways, bioavailability enhancement, and clinical efficacy may significantly strengthen the role of nutraceuticals in modern depression management. Overall, plant-derived nutraceuticals represent a promising multidimensional approach for improving mental health and advancing integrative strategies in the prevention and treatment of major depressive disorders.

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