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# Herbal Interventions as Promising Therapeutic for Alleviating Depression: A Comprehensive Review

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**ABSTRACT:** Depression is a global mental health challenge with significant social and economic burdens. While conventional pharmacological treatments have been the cornerstone in depression management, there is a growing interest in exploring alternative and complementary herbal therapies. Herbal interventions have emerged as promising therapeutic approaches for depression treatment. Both clinical and preclinical research has shown that individuals with depression often experience simultaneous activation of neuro-inflammatory response within immune system and heightened activity in hypothalamus pituitary-adrenal (HPA) axis of neuroendocrine system. These two systems interact with each other bidirectionally through neural, immunological and humoral mechanisms. This review article provides an outline of the current progress of research on herbal interventions, emphasizing their potential as emerging therapeutics for depression. It discusses the mechanisms of action, safety profiles, and evidence from clinical studies supporting the use of various herbal remedies. Herbal interventions and traditional Chinese formulations hold promise as a valuable adjunct or alternative to conventional treatments, offering new avenues for the comprehensive care of individuals with depression.

**KEYWORDS:** Depression, Chinese medicine, Herbal, therapeutic, signaling.

## 1. INTRODUCTION

The prevalence and comorbidity of depression affects a significant portion of the global population. According to statistical data, approximately 264 million individuals across the world are grappling with this debilitating condition its prevalence is substantial, with around 11.3% of adults experiencing depressive disorders on an annual basis [1]. This mental health concern characterized by the persistent feelings of utmost sadness, lack of interest in daily activities, and the overall impaired ability to function optimally [2]. The monoamine hypothesis that posits alterations in the levels of neurotransmitters viz. Serotonin, norepinephrine and dopamine play a fundamental role in the pathophysiology of the depression. Conventional antidepressants, as mentioned earlier, primarily target these monoamine systems. However, the limitations and side effects associated with these drugs have spurred research into herbal remedies that may exert their antidepressant effects through monoamine modulation [3]. The brain-derived neurotrophic factor (BDNF), in particular, has gained significant attention due to its role in promoting neuronal growth, survival, and plasticity. Reduced BDNF levels have been associated with depression, and interventions that increase BDNF expression hold promise as novel antidepressant strategies [4]. Preclinical investigations have demonstrated that an overactive hypothalamic-pituitary-adrenal (HPA) axis can trigger the initiation of the immune system's neuroinflammatory response. Conversely, neuroinflammation can also influence the functioning of the HPA axis through a range of underlying mechanisms [5]. Research conducted in clinical settings has revealed that individuals afflicted with depression exhibit notably elevated range of proinflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP) and inflammasomes in comparison to the individuals in good health. Also, these investigations have highlighted a heightened occurrence of depression among patients grappling with chronic peripheral inflammatory disorders [6]. Antidepressant medications, including selective monoamine reuptake inhibitors and fast-acting antidepressants that enhance glutamate transmission exhibit the capacity to ameliorate depressive mental states, these pharmaceuticals agents are considered less than optimal due to their significant side effects and relatively low effectiveness rates [7]. Herbal remedies can enhance serotonin receptor sensitivity or inhibit enzymes like monoamine oxidases, thereby demonstrating potential antidepressant properties [8].

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Chinese Herbal Medicine (CHM) frequently serves as a therapeutic approach capable of concurrently influencing multiple pharmacological targets. This medication approach, rooted in systems biology, employs a multi-target, multi-drug strategy that proves especially apt for addressing complex, genetically diverse, and multifaceted conditions like depression [9]. In Traditional Chinese Medicine (TCM) practice, a multitude of CHM formulations are presently employed in the treatment of depression. Clinical investigations have demonstrated that these CHM antidepressant concoctions yield similar levels of effectiveness as conventional antidepressants, while being associated with minimal adverse effects [10]. By exploring the potential benefits of herbal remedies as an alternative or adjunctive treatment, we aim to shed light on their efficacy, safety, and the mechanisms through which they may exert their therapeutic effects. This review could offer valuable insights into a more holistic approach to managing depression, potentially alleviating some of the limitations associated with conventional treatments.

## 2. PATHOPHYSIOLOGY OF DEPRESSION

Depression is a complex and multifaceted mental health condition with a range of potential causes and contributing factors. While the exact pathophysiology of depression is not fully understood, research has provided insights into the biological, psychological, and social mechanisms that may underlie this condition [11]. It is likely the result of a combination of these factors, and individual experiences of depression can vary widely. The complex and heterogeneous nature with multiple interconnected factors contributing to its pathophysiology. These factors interact in a dynamic way which makes it challenging to pinpoint a single cause. Understanding the multifaceted nature of depression is essential for developing effective strategy and interventions that address its various aspects, from neurotransmitter imbalances to psychosocial stressors[12].

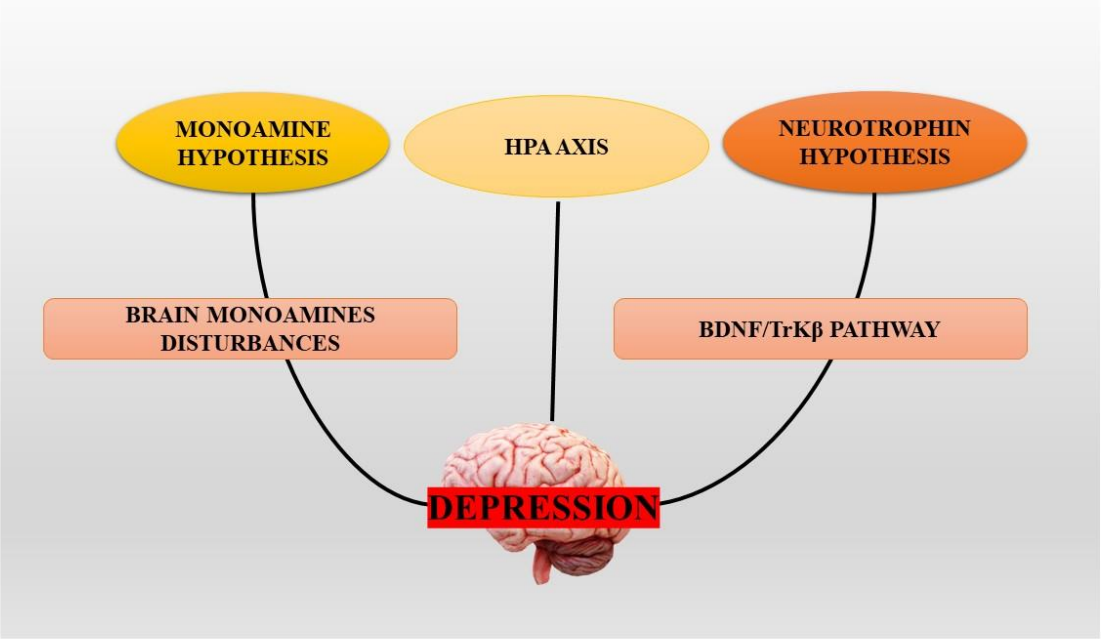


**Figure 1:** Figure illustrates the multifaceted pathophysiology of depression, highlighting key mechanisms. The monoamine hypothesis underscores neurotransmitter imbalances, the HPA axis activation represents stress-related hormonal dysregulation, and the neurotrophin hypothesis signifies altered neurotrophic support. Together, these factors contribute to the complex etiology of depression.

### 2.1. Monoamine Hypothesis

The monoamine hypothesis, a foundational theory in depression research, posits that dysregulation of neurotransmitters such as serotonin, norepinephrine, and dopamine underpins this intricate mental health disorder. These neurotransmitters, synthesized from precursor molecules, include tryptophan for serotonin, and tyrosine for norepinephrine and dopamine [13]. Upon nerve

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impulse propagation, neurotransmitters are released into the synapse and engage receptors on postsynaptic neurons. Transporter proteins, including the serotonin transporter (SERT) and reuptake mechanisms recycle unbound neurotransmitters back into presynaptic neurons Importantly, monoamine oxidase enzymes (MAO-A and MAO-B) are pivotal in breaking down excess neurotransmitters, with monoamine oxidase inhibitors (MAOIs) counteracting this process [14]. Addressing reuptake, selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine hinder reabsorption of serotonin, maintaining heightened synaptic levels. Activation of postsynaptic receptors triggers intracellular signaling pathways, notably cyclic AMP (cAMP), culminating in downstream effects such as gene expression modulation and synaptic plasticity. Over time, chronic disturbances in monoamine levels due to genetic susceptibilities or external stressors can disrupt neuroplasticity and weaken synaptic connections [15] This intricate chain of molecular interactions collectively contributes to mood dysregulation and the emergence of depressive symptoms.

### 2.2. Neurotrophic Hypothesis

The Neurotrophic Hypothesis in relation to depression focuses on the significant role of neurotrophic factors, with particular emphasis on Brain-Derived Neurotrophic Factor (BDNF), shaping underlying mechanisms of the disorder. BDNF, a crucial player in promoting neuronal growth, survival, and maintenance, holds sway over neural circuits central to mood regulation. This intricate cascade of molecular events unfolds as BDNF is synthesized within neurons and subsequently released into synapses in response to neuronal activity [16]. Binding to its TrkB receptors situated on neuronal surfaces initiates a cascade of events, including autophosphorylation of the TrkB receptors. These activations trigger a network of intracellular signaling pathways, encompassing Ras-MAPK and PI3K-Akt, with far-reaching implications for gene expression and synaptic plasticity. Through these mechanisms, BDNF underpins the fortification and persistence of neural circuits vital to mood regulation. Beyond its role in synaptic plasticity, BDNF contributes to neuronal survival and supports the emergence of new neurons, a process called neurogenesis [17]. The significance of BDNF in depression emerges from consistent observations of lowered BDNF levels in depressed individuals. This reduction in BDNF signaling potentially impairs neuroplasticity and the health of brain regions associated with mood. Chronic stress, a known factor in depression, can lead to decreased BDNF expression and function, potentially exacerbating depressive symptoms [18]. Therapeutically, interventions aimed at augmenting BDNF expression and signaling hold promise as strategies for addressing depression, encompassing physical activity, social engagement, and specific antidepressant medications.

### 2.3. Hypothalamic-Pituitary-Adrenal (HPA) Axis

Hypothalamic-Pituitary-Adrenal Axis, a central element of stress response system, emerges as a pivotal player in the context of depression. Its intricate workings lie at the intersection of neural and endocrine systems, influencing mood regulation and mental well-being. In response to perceived stressors, the HPA axis engages in a precisely choreographed molecular cascade. It commences with hypothalamus releasing corticotropin-releasing hormone (CRH) that in turn prompts anterior pituitary to secrete adrenocorticotropic hormone (ACTH). Subsequently, the ACTH travels through the bloodstream to the adrenal glands, situated atop the kidneys, instigating the release of cortisol and other stress hormones [19]. Cortisol, often referred to as the body's primary stress hormone, exerts its influence through interactions with various receptors, notably the glucocorticoid receptors (GRs), which are abundant in the brain, including regions associated with mood regulation. While cortisol's role in helping the body respond to stress is crucial, chronic or excessive activation of the HPA axis may lead to dysregulation. In the context of depression, this manifests as persistent elevation of cortisol levels. At a molecular level, prolonged cortisol exposure can result in structural and functional changes in brain areas like the hippocampus and prefrontal cortex, which are vital for mood regulation, cognition, and emotional processing. Furthermore, cortisol can influence neurotransmitter systems, particularly serotonin and dopamine, which are integral to mood regulation [20]. Dysregulation of these systems can lead to the emergence of depressive symptoms. The HPA axis operates within a tightly controlled feedback loop. Elevated cortisol levels can inhibit the release of CRH and ACTH, aiming to restore equilibrium. However, chronic stress and prolonged HPA axis activation can disrupt this balance, contributing to a heightened vulnerability to depression [21]. The intricate interplay between the HPA axis, stress hormones, neural circuits, and neurotransmitter systems underscores its significance in the etiology of depression. This understanding offers potential avenues for therapeutic interventions, emphasizing the importance of stress management and modulating HPA axis activity to alleviate depressive symptoms.

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## 3. PATHWAYS LINKED IN DEPRESSION

### 3.1. Inflammatory Pathways

The association between Inflammatory Pathways and depression has garnered increasing attention due to mounting evidence suggesting a significant link. This connection revolves around the chronic activation of the immune system and the heightened presence of proinflammatory cytokines observed in individuals experiencing depression [22]. At the molecular level, this cascade begins with the persistent activation of immune cells, which release proinflammatory cytokines like interleukin-6 (IL-6) into the bloodstream. These cytokines then interact with receptors on various cells, including neurons in the brain. Particularly, the IL-6 pathway emerges as a key player, as IL-6 binding to its receptors initiates intracellular signaling events. Activation of these pathways can contribute to changes in neural functioning and connectivity, ultimately affecting mood regulation [23]. Importantly, proinflammatory cytokines can also impact the levels of neurotransmitters such as serotonin, dopamine and the glutamate, all are critical for mood and emotional regulation. This intricate interplay between inflammatory processes and neurotransmitter systems can collectively contribute to the emergence and persistence of depressive symptoms. Understanding the molecular signaling cascade within these inflammatory pathways offers insights into the complex interaction between the immune system and the central nervous system, shedding light on potential therapeutic targets for depression that involve modulating inflammation.

### 3.2. Glutamatergic Pathway

As the brain's primary excitatory neurotransmitter system, glutamate not only facilitates neural communication but also crucially shapes neural plasticity, cognition, and emotion regulation. Emerging evidence highlights disruptions in glutamate signaling and its associated cascade as contributors to the onset and progression of depression [24]. Abnormalities within this pathway, particularly concerning N-methyl-D-aspartate (NMDA) receptor-mediated processes, set in motion a sequence where glutamate binding prompts calcium influx, activating intracellular kinases and transcription factors. These molecular events ultimately modulate the strength of synaptic connections, pivotal for efficient neural communication [25]. During the progression of depression, chronic stress and other factors can lead to maladaptive changes in synaptic plasticity and neural circuitry. These alterations, stemming from dysregulated glutamatergic signaling, manifest as dendritic atrophy, diminished synapse density, and compromised neuronal resilience, collectively disrupting the intricate balance of excitatory and inhibitory neurotransmission, thereby contributing to mood dysregulation and depressive symptoms [26]. Importantly, glutamate signaling interfaces with other pathways implicated in depression, such as the neurotrophic hypothesis and the monoamine system, influencing factors like brain-derived neurotrophic factor (BDNF) expression and release/reuptake of the monoamine neurotransmitters. The novel success of treatments like ketamine, an NMDA receptor antagonist, underscores the potential of transiently modulating glutamate signaling to swiftly ameliorate depressive symptoms by inducing synaptic changes that counteract the adverse adaptations seen in depression [27].

### 3.3. GABAergic Pathway

Gamma-aminobutyric acid (GABA), a primary inhibitory neurotransmitter in brain which play a pivotal role in progression of depression through intricate molecular signaling. GABAergic signaling, mediated by GABA-A and GABA-B receptors, regulates neural excitability and maintains the balance between excitation and inhibition. In depression, disruptions in GABAergic function, including reduced GABA levels and impaired receptor activity, lead to altered inhibitory tone, resulting in heightened neural activity within mood-regulating circuits [28]. This disruption cascades into effects on glutamatergic and monoaminergic pathways, contributing to excitotoxicity, neuroinflammation, and compromised neurotransmitter signaling. Chronic stress impacts GABAergic signaling, further perpetuating these abnormalities [29]. Targeting GABAergic dysfunction holds potential for therapeutic intervention in depression, with emerging research aiming to develop precise treatments that restore neural circuit equilibrium without the drawbacks of conventional medications. Understanding GABA's role sheds light on the intricate mechanisms underlying depression's progression and offers prospects for innovative treatment strategies.

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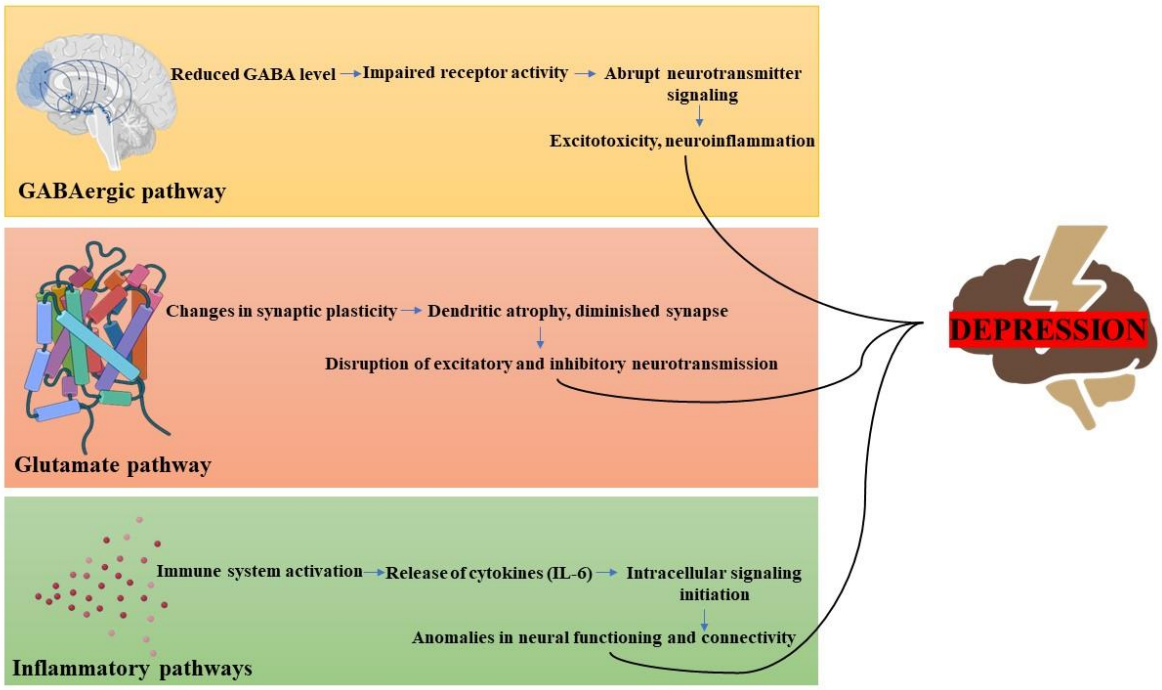


**Figure 2:** Pathways associated with depression, GABAergic pathway, which represents inhibitory neurotransmission, the glutamate pathway, indicative of excitatory neurotransmission, and the inflammatory pathway, reflecting immune system involvement. These pathways collectively contribute to the intricate landscape of depression pathogenesis.

## 4. HERBAL INTERVENTIONS FOR DEPRESSION AND MOOD DISORDERS

Herbal medicine has been greatly used for centuries across different cultures in order to treat wide range of health conditions, including mood disorders like depression [30]. While conventional medical treatments, such as psychotherapy and prescription medications, remain the primary approaches for managing depression, some individuals turn to herbal remedies as alternative or complementary options [31]. Here are some herbal remedies that have been traditionally used for managing depression and mood disorders.

### 4.1 Saffron

Saffron, renowned as a highly prized spice, holds a traditional history of utilization in culinary contexts. Recent investigations into saffron have revealed a range of therapeutic properties. In the domain of Persian traditional medicine, saffron has been employed for the management of depression, noted for its lack of adverse effects. Saffron therapy has demonstrated potential in inhibiting the reuptake of serotonin by nerve cells, suggesting a possible avenue for addressing mild to moderate depression [32]. The active constituents present in saffron's corms, particularly within the petroleum ether and dichloromethane fractions, exhibit properties resembling those of antidepressants. These findings underscore the potential of Crocus sativus, also known as saffron crocus or the autumn crocus in mitigating mild to moderate depression. Integral components of saffron, notably Crocin and Safranal, assume a critical role in modulating various neurotransmitter organizations in the brain these encompass serotonin, dopamine, glutamate and the norepinephrine thereby contributing to the reduction of depression [33]. Importantly, saffron dosages have demonstrated efficacy comparable to antidepressants like fluoxetine and imipramine [34].

### 4.2 Rhodiola (*Rhodiola Rosea*)

Rhodiola (*Rhodiola Rosea*), which is a perennial plant also known as the roseroot, has an old history of use to enhance both physical endurance and cognitive performance. Originating from regions such as Asia and Eastern Europe, this herbal remedy has garnered attention for its potential in the treatment of depression. R. Rosea has exhibited the ability to elevate endogenous β-endorphin levels, contributing to its potential in addressing depression [35]. A comparison between the Rhodiola crude extract and

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standard antidepressant for treating mild to moderate type of depression revealed that *Rhodiola rosea* is far better tolerated than sertraline drug, indicating the potential as an alternative treatment option for the patients of depression [36]. The influence of *Rhodiola rosea* extends to the modulation of biogenic monoamines, including dopamine, serotonin and the norepinephrine, in brain. Extracts from *Rhodiola rosea* inhibit the activity of these two, MAO-A and MAO-B (Monoamine oxidase-A and Monoamine oxidase-B), thereby enhancing permeability of BBB (blood-brain barrier) [37]. Additionally, the impact of extract on the neuropeptide-Y (NPY) leads to fast upregulation of heat shock protein called Hsp-70. Which in turn, results in the suppression of stress induced JNK protein, influencing glucocorticoid receptors and the cortisol levels [38]. The effects of *Rhodiola rosea* extend up to the mediation of stress response, regulation of homeostasis in HPA axis activity and also the modulation of G-protein-coupled receptor (GPCR) signaling pathway, along with other molecular networks implicated in the depression [39]. As suggested by various studies, Rhodiola holds promise as a valuable adjunct in the management of depression.

**4.3 Berberine**

Berberine is a natural isoquinoline alkaloid, occupies a significant position within traditional Chinese medicine and derives from various herbal species such as *Berberis hydrastis canadensis* (golden seal), *Tinospora cordifolia* and *Phellodendron amurense* (Amur cork tree) [40]. Berberine showcases a wide range of effects pertinent to depression, encompassing the inhibition of the monoamine oxidase activity, modulation of α2 autoreceptors, regulation of NOX and ROS, rise of 5-HT and DA levels, antagonism of D2 receptors and the agonism of D1 [41]. It also interacts with substances like substance P and sigma receptors, as well as the l-arginine-NO-cGMP pathway [42]. Berberine's involvement extends to factors such as tumor necrosis factor β, interleukin-6, interleukin-1-beta as well kynurenine levels. It contributes to the reduction in the lipid peroxide and superoxide dismutase range, induces NGF secretion and activates pathways including phosphoinositide 3-kinase/protein kinase/nuclear factor-E2-related factor 2-mediated regulation, BDNF-cAMP response element binding protein and eEF2 pathway [43]. Furthermore, Berberine offers gastrointestinal protection, leads to reduction in the plasma corticosterone level and impacts fluctuations in gonadal hormones [44]. However, the limitation of berberine's restricted bioavailability poses a significant obstacle in its application and development [45].

**4.4 Flavanones**

Scientific research has shed light on the potential, neuroprotective and antidepressant effects associated with dietary flavanones. Among these dietary compounds, naringenin (NAR), a natural flavanone found in peels of the citrus fruits possesses antioxidative properties, alongside demonstrating antidepressant [46]. Flavonoids, naturally occurring compounds, have demonstrated the remarkable ability to combat and even reverse stress through a range of mechanisms. Over recent decades, extensive research has delved into the antidepressant properties of these natural chemicals, particularly flavonoids, which exhibit multiple beneficial effects on the brain. Numerous preclinical studies have revealed that specific flavonoids hold promise as potential antidepressants, as they have been shown to alleviate depressive behaviors in animal models. These compounds achieve their antidepressant effects by boosting the levels of various neurotransmitters, promoting the expression of neurotrophic factors, and enhancing neurogenesis in the brain. This not only underscores the potential of flavonoids in the realm of mental health but also highlights their significance as natural remedies for combating stress and depression [47]. Several isolated flavonoids have been reported to reverse low levels of BDNF and to have antidepressant properties by boosting BDNF expression. Hesperidine, apigenin, astilbin, baicalein, chrysin, dihydromyricetin, hyperoside, naringenin, orientin and the 3,5,6,7,8,3′,4′-heptamethoxyflavone are among the flavonoids [48]. These flavonoids have been shown in pre-clinical research to raise hippocampus BDNF levels, neuronal plasticity, neurogenesis and synaptogenesis in the mouse brain. These flavonoids, unlike pharmaceutical antidepressants, were discovered to inhibit both stress-induced and corticosterone-mediated decreases in BDNF expression [49].

**4.5 Curcumin**

Curcumin is the crucial curcuminoid found in the turmeric (*Curcuma longa*), possesses remarkable anti-inflammatory and antioxidant characteristics, commonly used as a spice in the dietary practices of Asian populations, particularly in countries like India and China [50]. Curcumin exhibits effects reminiscent of those observed with conventional antidepressants such as fluoxetine and imipramine. It results in the enhancement of serotonin and dopamine levels, while also facilitating an increase in brain-derived neurotrophic factor (BDNF) [51]. Moreover, curcumin functions by inhibiting the enzymes monoamine oxidase A

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and B, leading to elevated neurotransmitter levels in the brain. It additionally suppresses activity of inflammatory cytokines including NLRP3 inflammasome and interleukin-1B [52]. Curcumin's anti-inflammatory properties have been established in both animal and human studies. Curcumin was found to lower CRP and high-sensitivity CRP concentrations in various meta-analysis of clinical trials [53]. Additionally, there is proof that curcumin can prevent glutamate-induced neurotoxicity by influencing NMDA receptor activity by increasing the expression of the GluN2A subunit and promoting the phosphorylation of the GluR1 subunit of the AMPA receptor [54].

## 5. CHINESE HERBAL MEDICINE (CHM)

Chinese Herbal Medicine has long been increasingly recognized for their potential role in the management of depression, offering a complementary approach to conventional treatments. Several studies have explored the use of CHM in depression, shedding light on its mechanisms of action and therapeutic benefits [55]. CHM formulations typically consist of a combination of herbs, and their efficacy is attributed to a synergistic effect of multiple bioactive compounds. One of the primary mechanisms by which CHM exerts its antidepressant effects is through the modulation of neurotransmitters, particularly serotonin and norepinephrine [56]. Compounds found in CHM formulations have been shown to influence the reuptake and metabolism of these neurotransmitters, similar to conventional antidepressant medications. Moreover, CHM is believed to possess anti-inflammatory and antioxidant properties, which can counteract the neuroinflammatory processes often associated with depression [57]. Clinical studies have provided evidence of the effectiveness of CHM in alleviating depressive symptoms. For instance, a meta-analysis of randomized controlled trials (RCTs) revealed that CHM was found to be more effective than the placebo in reducing depressive symptoms. Moreover, CHM was associated with fewer adverse effects compared to some conventional antidepressant drugs [58]. However, the quality of evidence varies among studies, and more high-quality RCTs are needed to establish CHM's efficacy conclusively. Chinese Herbal Medicine holds promise as a complementary approach in the treatment of depression. Its multifaceted mechanisms of action, which involve neurotransmitter modulation, anti-inflammatory properties and antioxidant properties, make it a potentially valuable option, especially for individuals who may not respond well to conventional treatments or are concerned about side effects.

### 5.1 Banxia Xiexin decoction

Banxia Xiexin decoction is the traditional Chinese medicinal formulation renowned for its application in addressing diverse health conditions. Comprising several distinct herbs like Banxia, Ganjiang, Scutellaria, ginseng, liquorice and jujube [59]. This decoction has garnered attention for its therapeutic potential and biological mechanism centers on the modulation of cytokines and inflammatory mediators via HIF-1α, contributing to its effectiveness in managing depression [60]. Beyond its role in depression treatment, Banxia Xiexin decoction actively influences drug and lipid metabolism, as well as orchestrating the functions of nervous system, immune system and digestive system [61]. This comprehensive impact extends its potential application to treating various other disorders in a similar manner.

### 5.2 Sihogayonggolmoryeo-tang (SGYMT)

Sihogayonggolmoryeo-tang (SGYMT), also known as Chai-Hu-Jia-Long-Gu-Mu-Li-Tang, has its origins deeply rooted in traditional medicine. This formulation consists of distinct herbs, which encompass Bupleuri Radix, Pinelliae Rhizoma, Cinnamomi Ramulus, Scutellariae Radix, Jujubae Fructus, Codonopsis Radix, Ostreae Concha, Zingiberis Rhizoma Recens and Rhei Rhizoma [62]. Contemporary research has shed light on SGYMT's potential in addressing major depressive disorder (MDD) and post-stroke depression (PSD) [63]. Additionally, a randomized controlled trial involving human participants showed promising results, with SGYMT administration leading to significant improvements in depressive symptoms compared to a placebo group [64]. These findings suggest that SGYMT may hold potential as an adjunctive or alternative therapy for depression, although further clinical trials and mechanistic research are needed to validate its efficacy and safety in humans and elucidate the underlying mechanisms of action.

### 5.3 Kaixinjieyu

Kaixinjieyu represents an effective Chinese herbal medicine specifically intended for addressing vascular depression, a distinct form of the late-life depression, is intimately associated with the vascular conditions and also cerebrovascular risk factors. K.J.

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exerts its antidepressant effects by coordinating the enhancement of neurogenesis, reinforcing the integrity of tight junctions with brain-blood barrier, promoting balance with fibrinolytic system [65]. K.J. treatment led to significant enhancements in several measures, including an increased preference for sucrose, greater distance traveled, more frequent rearing behavior, and improved blood flow in the cortex. Additionally, the functions of the neurovascular unit (NVU), as assessed by the levels of brain derived neurotrophic factor (BDNF), tropomyosin receptor kinase B (TrkB), tissue plasminogen activator (t-PA) and mRNA, as well as the expression of zona occludens protein-1 (ZO-1), occludin, and claudin-5 proteins, all showed significant increases. On the other hand, the levels of plasminogen activator inhibitor-1 (PAI-1) and matrix metalloproteinase-2 (MMP-2) proteins and mRNA, along with the rates of neuronal apoptosis, exhibited significant decreases following K.J. treatment [66].

**5.4 Lavandula angustifolia Mill**

*Lavandula angustifolia* Mill, commonly known as Lavender and a member of the Lamiaceae family, is an aromatic, evergreen herb originating from Mediterranean region [67]. Its therapeutic attributes encompass addressing mood disturbances such as restlessness or insomnia, as well as alleviating symptoms of nervous stomach irritation and intestinal discomfort. These properties contribute to enhancing the resilience of the nervous system, ultimately aiding in mitigation of depression and nervous exhaustion [68]. Lavender displays antidepressant activity with a reduced incidence of side effects compared to fluoxetine [69]. Lavandula is also recognized for its efficacy in addressing gastric issues and relieving headaches, particularly tension headaches. This herb possesses properties that make it useful as an antispasmodic, pain reliever, and muscle relaxant [70]. Furthermore, clinical studies have provided evidence of its positive impact in managing sleep disturbances and anxiety [71]. Given the growing interest in herbal remedies and *Lavandula angustifolia's* known antidepressant and calming properties, the research findings indicate the potential utilization of this herb in individuals with depression. This could lead to achieving a more rapid onset of antidepressant effects and potentially reducing the side effects associated with chemical antidepressant medications like citalopram.

**5.5 St. John's Wort (Hypericum perforatum)**

*Hypericum perforatum*, also called as the St. John's wort (SJW), is medicinal plant renowned for its significant antidepressant properties. This extensively studied plant exhibits documented pharmacological actions that encompass not only its antidepressant effects but also antiviral and antibacterial attributes [72]. Extract from *Hypericum perforatum* L. St. John's wort is recognized as an effective standard treatment for depression. Consequently, significant efforts have been directed towards identifying the specific active compounds responsible for its antidepressant effects. From a phytochemical perspective, St. John's wort stands out as one of the most extensively studied medicinal plant. Researchers have identified range of several bioactive compounds in raw plant materials which include flavonol derivatives, proanthocyanidines, xanthones, phloroglucinols and the naphthodianthrones [73]. The primary focus of research on St. John's wort has revolved around its pharmacological activity as an antidepressant. Numerous reports have indicated its superior effectiveness compared to a placebo and similar efficacy when compared to various antidepressant medications. However, the exact mechanism responsible for St. John's wort's antidepressant activity remains unclear, especially regarding its most significant constituents. Some in vitro studies suggested that hypericin might contribute to antidepressant effects by inhibiting monoamine oxidase (MAO) enzyme [74].

**5.6 Ginseng**

Ginseng occupies a prominent position in the realm of herbal medicine, boasting a history spanning millennia in East Asian nations like China, Japan, and Korea [75]. The longstanding use of ginseng can be attributed to its natural antioxidant properties. Ginsenosides, derived from various parts of the ginseng plant such as the roots, leaves, stems, and fruit, encompass a wide range of distinct categories. Numerous researches have highlighted multifaceted pharmacological effects of the ginsenosides. They have demonstrated efficacy in treating organ damage, preventing cell death, and addressing immunological and metabolic disorders [76]. These biologically active components have also been shown to support processes like neurogenesis, synaptogenesis, neuronal growth, and neurotransmission, thereby contributing to the safeguarding of the central nervous system against unforeseen challenges. Ginseng is also known for its potential in enhancing memory [77]. Ginseng has the ability to enhance an individual's response to a stressful environment by effectively managing the functioning of the HPA axis. Moreover, it extends its utility beyond everyday consumption among individuals in good health. Ginseng presents itself as a promising therapeutic option for individuals dealing with HPA axis disorders, particularly those characterized by excessive cortisol secretion, such as

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depression, asthma, hypertension, and post-traumatic stress disorder (PTSD) [78]. Ginseng has been shown to effectively mitigate stress, a significant contributor to depression. Studies involving animal models have confirmed this stress-reducing property of ginseng. Importantly, ginseng's performance in these experiments was on par with that of the widely marketed antidepressant namely fluoxetine, in terms of its effectiveness [79]. Additionally, ginsenoside Rg1 contributes to the upregulation of the SIRT1-MAPK signaling pathway, resulting in the reduction of NF-κB transcriptional activity [80]. Moreover, ginsenosides play a role in downregulating Akt and mTOR [81]. As a result, the potential of ginsenosides for treating depression becomes evident.

**5.7 Lion's mane mushroom (*Hericium erinaceus*)**

*Hericium erinaceus* which is a well-known edible mushroom, has established itself a traditional medicinal resource in various Asian countries, employed to address a range of ailments [82]. The therapeutic attributes of *Hericium erinaceus* encompass the stimulation of diverse neurotrophic factors and monoamines, in addition to the modulation of inflammatory responses. Both the mycelia and fruiting bodies of *H. erinaceus* linked to the activation of the neurotrophic factor NGF via the JNK pathway. Moreover, it inhibits monoamine oxidase (MAO), resulting in the upregulation of crucial monoaminergic neurotransmitters like serotonin, norepinephrine, and dopamine. Through the reduction of pro-inflammatory factors like IL-6, TNF-α, and NF-κB, coupled with the elevation of BDNF levels, Hericium erinaceus exhibits antidepressant effects [83]. This mushroom also showcases anti-oxidative and anti-inflammatory properties, rendering it suitable for addressing cognitive impairment [84]. After *H. erinaceus* administration, there was a considerable increase in blood pro-BDNF levels but no change in serum BDNF [85]. While further research is necessary to validate its antidepressant effects and compare them with conventional antidepressants, the potential of *Hericium erinaceus* as an alternative treatment for depression is noteworthy.

**Table 1:** Comprehensive insight into different herbal intervention, their mode of action and geographical distribution in context to depression.

| Herbal Intervention | Geographical Distribution | Mode of Action |
|---|---|---|
| Saffron | Mediterranean region, Iran, India | Antioxidant, serotonin modulation |
| Rhodiola | Northern Europe, Asia | Adaptogenic, neurotransmitter regulation |
| Berberine | Various regions, including China | Neuroprotective, anti-inflammatory properties |
| Flavanones | Abundant in citrus fruits worldwide | Antioxidant, anti-inflammatory properties |
| Curcumin | South Asia, especially India | Anti-inflammatory, neuroprotective properties |
| Banxia Xiexin Decoction | China, Traditional Chinese Medicine | Brain lipid metabolism via downregulation of LPC levels |
| Sihogayonggolmoryeo-tang (SGYMT) | Korea, Traditional Korean Medicine | Multifaceted herbal formula |
| Kaixinjieyu | China, Traditional Chinese Medicine | Up-regulation of neurogenesis and balance of the fibrinolytic system. |
| Melissa officinalis L | Europe, Asia, North America | Anxiolytic, GABAergic effects |
| Lavandula angustifolia Mill | Mediterranean region, worldwide | Anxiolytic, sedative effects |
| Echium amoenum | Iran, Mediterranean region | Potential serotonin modulation |
| Hypericum perforatum | Europe, North America | Serotonin reuptake inhibition, anti-inflammatory |
| Ginseng | East Asia, North America | Adaptogenic, mood stabilization |
| Lion's Mane Mushroom | Asia, North America | Neurotrophic factors stimulation |

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## 6. DISCUSSION

Depression is one of the complex mental health condition that affects millions of people severely worldwide. It is mainly characterized by the persistent feelings of sadness, hopelessness and loss of interest in activities on daily basis. While conventional treatments such as psychotherapy and pharmaceutical medications have proven effective for many individuals, there is a growing interest in exploring the potential of herbal medicine as an alternative or complementary approach to treating depression. Herbal medicine has a long history of use in various cultures for managing mood and mental health. Some herbal remedies have shown promise in addressing symptoms of depression. For example, St. John's Wort (*Hypericum perforatum*), a widely studied herb, has been found to have mild antidepressant effects. It is believed to work by affecting neurotransmitters in the brain, particularly serotonin, which plays a key role in regulating mood. The effectiveness of herbal remedies can vary from person to person and their safety and efficacy should be thoroughly researched and discussed with a healthcare professional before use. The future prospects of herbal medicine for depression treatment are intriguing. As the field of alternative and complementary medicine continues to gain recognition and acceptance, there is growing interest in conducting rigorous scientific studies to better understand the mechanisms and effectiveness of herbal treatments. This could lead to the development of standardized herbal preparations that are consistent in quality and dosage, making them a more reliable option for individuals seeking natural remedies for depression. Furthermore, the potential benefits of herbal medicine extend beyond just symptom management. Many herbal remedies are associated with fewer side effects compared to pharmaceutical drugs, which can be appealing to those who want to avoid the adverse effects commonly associated with antidepressant medications. Additionally, the holistic approach of herbal medicine, which often considers the overall well-being of the individual, aligns with the growing trend towards personalized and integrative healthcare. However, it's important to exercise caution and remain critical when considering herbal remedies for depression. Not all herbs are safe or effective, and they can interact with other medications or health conditions. Therefore, individuals experiencing depression should consult with a qualified healthcare provider or herbalist who can assess their unique circumstances and provide guidance on the appropriate use of herbal medicine as part of a comprehensive treatment plan. Herbal medicine holds promise as a potential treatment option for depression, both as an alternative and a complement to conventional therapies. Future research may uncover new herbal remedies and better define their mechanisms of action. However, until more evidence is available, individuals seeking herbal treatments for depression should do so under the guidance of qualified healthcare professional to ensure the safety and effectiveness. As our understanding of the therapeutic potential of herbs continues to evolve, herbal medicine may play an increasingly valuable role in addressing the complex challenges of depression.

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