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Recent advancements in digital and traditional treatment strategies for major depressive disorder using medicinal herbs

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ABSTRACT

Integrating digital health technologies, including mobile applications and digital biomarkers, with traditional medicinal plants and phytochemicals may enhance the effectiveness of standard antidepressants. Mechanisms through which phytochemicals and digital health tools may alleviate depression are described based on currently known mechanisms. Traditional medicinal plants and phytochemicals may enhance the efficacy of standard antidepressants. This article provides an in-depth discussion of the known mechanisms through which phytochemicals and medicinal herbs may alleviate depression, and examines the diagnostic, preventive, and treatment practices for major depressive disorder (MDD), focusing on integrating digital innovations and phytotherapy.

1 Introduction

Depression is a neurological disorder that leads to significant morbidity and mortality [1]. Major depressive disorder (MDD) is the leading cause of disability worldwide. The symptoms include loss of appetite, fatigue, and weight loss. However, feelings of guilt, low self-esteem, lack of interest or pleasure, intense exhaustion, difficulties with sleeping or eating, and trouble concentrating may contribute to suicide [2]. This potentially lethal mental illness is a major cause of adult disability. According to the World Health Organization (WHO), the prevalence of depression and other mental disorders is increasing globally, particularly in low-income countries. This trend coincides with rising life expectancy, and more individuals reach the age at which they commonly develop [3]. MDD, a leading cause of disability, affects nearly 300 million people worldwide. MDD was the third most burdensome disease in 2018 and is projected to become the most burdensome by 2030 [4]. Factors like low income, unemployment, bereavement, relationship breakdown, physical and mental illness, and substance abuse are strongly associated with increased depression rates globally.

Depressive disorders are treated with a variety of medications, including monoamine oxidase inhibitors, antidepressants, norepinephrine, selective serotonin reuptake inhibitors, dopamine reuptake inhibitors, serotonin antagonists, and other reuptake inhibitors [5]. Anxiety disorders are treated with pregabalin, tricyclic antidepressants, buspirone, benzodiazepines, monoamine oxidase

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inhibitors, and selective serotonin and norepinephrine reuptake inhibitors [6]. However, due to side effects or significant delays in efficacy, patients often do not adhere to these synthetic antidepressant regimens. Headaches, erectile dysfunction, addiction, seizures, and suicidal thoughts are among the serious adverse effects associated with synthetic antidepressants [7]. Due to the complexity of its pathogenic mechanisms, there are limited effective diagnostic methods and pharmaceutical treatment options for MDD. The pathogenesis of MDD has been elucidated through various hypotheses like the social-psychological hypothesis, the monoamine and inflammatory hypothesis, the neural circuit and function brain remodelling hypothesis, and the genetic and epigenetic anomaly hypothesis [8]. The initiation of relevant clinical studies has resulted in significant strides in identifying new pharmaceutical treatments, diagnostic criteria, and non-pharmacological preventive interventions for MDD in the last several years. The majority of patients are reluctant to take the medication due to its adverse effects, according to clinical research. Additionally, research indicates that some medications are effective for half of patients and that others fail to go into full remission [9].

Psychedelics have recently been discovered to induce significant changes in human mood and perception [10]. Lysergic acid diethylamide (LSD), N,N-dimethyltryptamine (DMT), and psilocybin are all members of a class of chemicals that bind to the 5-hydroxytryptamine 2A receptor (5-HT2AR) and activate it without preferentially selecting for any particular subtype of the receptor. The principal mediator of the acute subjective effects of psychedelics on cognition is the 5-HT2AR, which is expressed throughout the cortex [11].

Herbal medicine, known for its reduced side effects and lower cost, is another area of active research today [12]. Consequently, there has been significant interest in medicinal plants as a potential additional medication or even an alternative treatment for depression on a global scale due to their diverse range of therapeutic effects [13].

Such new avenues could enhance efficacy and facilitate integration through digital health technologies, such as mobile applications for mood tracking and wearable sensors for monitoring physiological changes. This facilitates real-time monitoring, enabling therapeutic approaches to be promptly adjusted based on patient feedback and biomarker information. Advances are also being made in deciphering the complexity of MDD pathogenesis through digital technologies such as neuroimaging and artificial intelligence. For example, artificial intelligence (AI) analysed brain scans can reveal how phytochemicals affect neuroplasticity, potentially leading to the discovery of new biomarkers for depression treatments [14].

This review article aims to investigate the potential of phytochemicals and medicinal herbs in alleviating MDD symptoms and their integration with emerging digital health technologies to enhance therapeutic outcomes. Given that depression is the most common cause of disability worldwide and that the pharmacological interventions in place have side effects and limited efficacy, this article delves into alternative solutions by examining the combination of traditional phytotherapy with digital innovations. This includes mobile mood-tracking applications, real-time physiological monitoring via wearable devices, and AI-driven personalisation of treatment protocols. This article attempts to compile the latest research on the mechanisms underlying the pathogenesis of depression, as well as emerging therapeutic interventions in highlighting strategies for improved diagnosis, prevention, and treatment of MDD. The work represents a significant advancement in the current literature by focusing on the convergence of traditional herbal medicine and digital health technologies to treat MDD. Unlike previous studies, this paper emphasises the need to integrate standalone phytotherapy with digital tools. Further research into emerging applications involves virtual reality (VR)-assisted anxiolytic herbal therapies, real-time biofeedback, and wearable sensors designed to enhance the therapeutic effectiveness of phytomedicines. This article bridges the gap between age-old remedies and precision medicines, contributing to developing personalised, scalable, and patient-centric management models for depression. This approach has not been extensively explored in previous research.

2 Pathogenesis and hypotheses of depression mechanism

Figure 1 illustrates the pathogenesis of depression. However, the exact cause of MDD remains unknown. Nonetheless, the pathogenic factors commonly associated with MDD include genetics, stress, and co-morbidities. In MDD patients, synaptic clefts lack sufficient levels of the monoamine neurotransmitters norepinephrine (NE), 5-hydroxytryptamine (5-HT), and dopamine (DA). The investigated antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors (SNRIs), work primarily by blocking their reuptake. Increased levels of proinflammatory cytokines, particularly interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6, indicate that the inflammatory-immune response is linked to the development of MDD [15]. In the pathological state of MDD, the expressions of neural cell marker proteins, such as glial fibrillary acidic protein (GFAP), connexin 30/43 (Cx30/43), S100 calcium-binding protein B (S100B), and aquaporin-4 (AQP4), are reduced. Astrocytes convert kynurenine (KYN) into the beneficial metabolite kynurenic acid (KYNA), whereas microglia convert it into the neurotoxic metabolite quinolinic acid (QUIN). In the brains of MDD patients, KYNA levels

are low, whereas QUIN levels are elevated. Inflammatory mediators, such as IL-6 and interferon (IFN)-γ, are produced when stressful conditions affect gut flora. Alterations in the microbiota can produce toxic QUIN or proinflammatory cytokines to activate the N-methyl-D-aspartate receptors (NMDARs), which can subsequently cross the blood-brain barrier (BBB). Ammonia levels in the brain rise due to impaired liver function [16]. Further research is needed to investigate the cellular pathological alterations in glial cells and the systemic pathogenic factors originating from different organs to better understand MDD's aetiology.

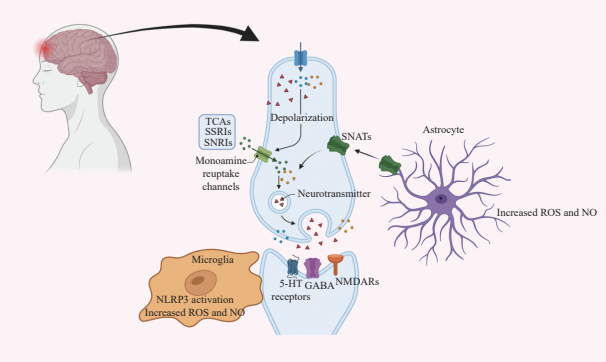

Figure 1 Interactions among organs, synapses, astrocytes, and microglia in the development of MDD
SNATs, sodium-dependent neutral, amino acid transporters. ROS, reactive oxygen species. NO, nitric oxide. NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3.

To gain a deeper understanding of the cellular and molecular processes behind the anomalies in the shape and activity of the prefrontal cortex (PFC) and hippocampus, the neurotrophic theory of depression offers a helpful framework. Essentially, this theory attributes the disorder's aetiology to impaired neuroplasticity in these areas. The term "neuroplasticity" describes a set of biological mechanisms that enable the brain to modify and adapt to its surroundings. Reduced dendritic arbours and spine density in pyramidal neurones characterise neuroplasticity in MDD, a phenomenon observed in the PFC and hippocampus. Decreased neurogenesis, or the formation of new neurones in the dentate gyrus (DG), is another indicator of impaired neuroplasticity in the hippocampus.

The most common pathogenic causes of MDD include genetic factors, stress, and co-morbidities. Deficiencies in monoamine neurotransmitters may be the cause of MDD, according to the conventional monoamine theory. The pathophysiology of MDD is highly related to other aberrant increases in synaptic cleft neurotransmitters, including glutamate, gamma-aminobutyric acid (GABA), and adenosine triphosphate (ATP) in the release of proinflammatory cytokines, oxidative stress, and reduced neurotrophic factors can all arise from interactions between neurones and glial cells [17]. In MDD, disruptions in the microbiota-gut-brain axis have been observed [18]. One of the pathophysiological factors of MDD is liver malfunction, which leads to oxidative stress (OS) and neuroinflammation in the brain [19].

3 Digital health technologies and their synergistic effects on phytomedicines

Integrating digital health technologies with phytomedicines offers a transformative approach to managing MDD. Although the robust theoretical framework supports this convergence, empirical evidence is necessary to substantiate its efficacy and practical application. Recent studies have opened up promising avenues for exploration; however, they underscore the necessity for more comprehensive clinical trials and real-world data. The benefits of optimising the use of phytomedicine extend to real-time monitoring applications for physiological and psychological parameters through wearable technologies and mobile health applications. For instance, analysing data obtained from wearable devices previously correlated to bolstering stress resilience and mood stability, similar to the effects of adaptogenic herbs, could offer valuable insights [20]. AI-driven personalisation involves analysing biomarkers and customising treatments accordingly. AI algorithms can predict patient responses to herbal therapies and optimise dosages based on genetic, metabolic, and behavioural data. For example, curcumin and saffron, recognised for their anti-inflammatory and neuroprotective properties, can now be tailored to an individual's metabolic and genetic profile, enhancing efficacy while minimising side effects. This level of precision has not been attainable with traditional approaches, underscoring the novel application of AI in phytomedicine [21, 22]. VR platforms, designed to create a soothing environment, can complement the anxiolytic effects of herbs. A randomised controlled trial reported a significant reduction in anxiety and depressive symptoms among patients who participated in VR sessions [23]. This synergy demonstrates how digital technologies can augment the therapeutic effects of phytomedicines, providing a multi-dimensional approach to MDD treatment. However, growing empirical evidence suggests that digital health technologies, in conjunction with phytomedicines, have synergistic effects in treating MDD [24]. Integrating real-time monitoring, AI-driven personalisation, and VR-enhanced therapies represent major developments. Still, further robust clinical trials and standardisation efforts are necessary to fully harness this new treatment paradigm.

The integration of digital tools, particularly AI and machine learning, has revolutionised the field of herbal medicine by improving treatment efficacy and addressing long-standing challenges. These tools are being employed to analyse complex data, predict therapeutic

outcomes, and optimise formulations for specific conditions. Deep learning algorithms applied to visible-spectrum imaging can effectively identify medicinal plant species with high accuracy rates. For example, convolutional neural network (CNN) architectures have been successfully used to analyse leaf vein patterns and classify different plant species. Multi-scale function (MSF) CNN models have further improved the accuracy of plant leaf recognition tasks by integrating multiple learning branches to capture multi-scale features.

4 Recent advancements in conventional medications

A study suggests that individuals with the most severe depression are advised to start with SSRIs [25]. The most commonly prescribed SSRIs include escitalopram, sertraline, paroxetine, and fluoxetine. SSRIs function by disrupting synaptic 5-HT reuptake to deliver their pharmacological effects. SSRIs may boost the expression of brain-derived neurotrophic factors (BDNFs) by targeting tropomyosin-related kinase B (TrkB), which could explain their long-term therapeutic effects, as BDNF is crucial for neurones to develop and survive. Other studies support the recent discovery that fluoxetine acts as a 5-HT 2B receptor (5-HT2BR) agonist. In mice subjected to chronic mild stress (CMS), fluoxetine lowers aberrant behaviour and suppresses A1-reactive astrocytes. In primary culture, fluoxetine suppresses the activation of A1-reactive astrocytes through astrocytic 5-HT2BR signalling, independent of Gq protein and b-arrestin1.

The antidepressant effects of TCAs are attributed to changes in neurotransmitter levels brought about by the drug's interaction with these brain chemicals. TCAs exhibit their antidepressant effects by interfering with neurotransmitter reuptake. Nortriptyline can inhibit 5-HT reuptake as well as NE reuptake, and it also exhibits central anticholinergic effects. Amitriptyline, imipramine, and desipramine are medications that severely inhibit 5-HT reuptake. Clomipramine, on the other hand, specifically inhibits NE reuptake [26]. Furthermore, TCAs can increase the release of NE and DA in cortical areas by antagonising 5-HT2AR and 5-HT2C receptor (5-HT2CR). Histamine receptors, particularly H1 receptors, can also bind to TCAs. Individuals with depression who have trouble sleeping may find relief from their symptoms if these medications induce drowsiness and sedation by inhibiting H1 receptors. Aside from the well-established pharmacological pathways, recent research indicates that amitriptyline can activate the fibroblast growth factor receptor (FGFR), which in turn produces glial cell line-derived neurotrophic factor (GDNF). Along with alleviating depression, amitriptyline can boost astrocyte gap junction intercellular communication (GJIC) by increasing the expression of Cx43. These findings suggest that TCAs have the potential to alleviate severe depression through astrocyte-based mechanisms that are somewhat independent of the monoamine system.

It is a common practice to prescribe SNRIs to MDD patients as a first line of defence. Two examples of SNRIs include venlafaxine and milnacipran. An elevated concentration of NE in the synaptic cleft results from SNRIs' inhibition of the NE transporter (NET), preventing NE from reabsorbing into presynaptic neurones. An intriguing observation is that rats treated with fluoxetine for an extended period have increased Cx43 expression in their PFC. This enhances the prevention of chronic unpredictable stress (CUS)-induced malfunctions in astrocytic gap junctions and the reversal of depressive-like behaviours induced by gap junction blocking [27].

TCAs can block the H1 receptors, which subsequently inhibits the protein kinase C (PKC) pathway. Additionally, by inhibiting DA transporters (DATs) in the presynaptic membrane, TCAs decrease dopamine reuptake and increase the concentration of dopamine in the synaptic gap [28]. This, in turn, increases the effect of dopamine on DA receptors (DARs) in the postsynaptic membrane [29]. Calcium/calmodulin-dependent protein kinase II (CaMKII) and IV (CaMK4) levels, together with cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) release, are elevated by activated DARs [30]. Another mechanism by which DA can activate DARs is through the cAMP-protein kinase A (PKA) route, which promotes CREB and BDNF levels through the mitogen-activated protein kinase (MAPK)/ extracelluar signal-regulated kinase 1 (ERK1)/2 pathway [31]. Inhibiting 5-HT reuptake by SERTs is a common mechanism of action for many antidepressants, including SSRIs, TCAs, and SNRIs. These medications increase 5-HT in the synaptic gap and activate 5-HTRs in the postsynaptic membrane to activate the cAMP-PKA pathway [32, 33]. Similarly, SNRIs, and TCAs also inhibit NET, leading to increased NE concentration between synapses, which in turn stimulates the postsynaptic membrane's cAMP-PKA pathway and enhances NE's effects on adrenoceptors. In addition to the adenylyl cyclase/cAMP/PKA pathway, NE impacts adrenergic receptors (ADRs) to induce TrkB-mediated Akt phosphorylation and mTORC1, which secretes post synaptic density protein 95 (PSD95) and glutamate receptor 1 (GluR1) [32]. Ketamine decreases glutamate release from GABAergic interneurons by blocking NMDAR. Consequently, GABA's inhibitory actions on the GABA receptor and the suppression of glutamate release from GABAergic interneurons are diminished. This leads to an increase in BDNF levels and the activation of the TrkB/protein kinase B (AKT)/mammalian target of rapamycin complex 1 (mTORC1) pathway [34].

5 Novel targets in depression

The exact pharmacological pathways of each drug are challenging to determine due to factors such as delayed

clinical efficacy, variability in therapeutic response among individuals, and difficulties in managing suicide risks. Clinical treatments for MDD primarily involve the use of antidepressants. Recently, several pharmacological compounds with antidepressant properties have been identified.

Psychedelics have the potential to provide rapid and long-lasting relief from depression. The classical hallucinogen psilocybin can exert its antidepressant effects by triggering the 5-HT2AR. Consequently, blocking the 5-HT2AR prevents psilocybin from exerting its antidepressant benefits and instead induces psychedelic behaviours in mice [35]. The results suggest that 5-HT2AR might not be the most effective pharmacological target for antidepressants. The hallucinogenic effects of lysergic acid diethylamide (LSD) and psilocybin are not addressed in another study, which suggests that a combination of these two substances may have long-term antidepressant effects through enhancing brain plasticity. When coupled, LSD and psilocybin can target 5-HT2AR, which biases the mediated signalling pathway and provides antidepressant benefits without hallucinations [36]. Since psilocybin's newly formed dendritic spines can transform functional synapses and remodel the medial frontal cortex of mice, synaptic rewiring may explain its rapid antidepressant effects. Isolating the hallucinogenic effects of psychedelics may contribute to the development of more targeted antidepressants with enhanced therapeutic potential [37].

Changes in TGF-β1 expression may be influenced by antidepressants, according to multiple studies. It has been demonstrated that sertraline, venlafaxine, fluoxetine, and paroxetine can raise TGF-β1 levels, which may contribute to their antidepressant effects [38]. There is evidence that venlafaxine can preserve neurones after a stroke by boosting astrocyte synthesis of fibroblast growth factor 2 (FGF-2) and TGF-β1 [39]. Next, research has demonstrated an increase in growth associated protein 43 (GAP-43) expression in rats' hippocampi after continuous desipramine treatment, which may affect neuronal plasticity in the central nervous system. Consequently, GAP-43 has been proposed as a potential target for antidepressant therapies [40].

Ketamine, a non-competitive NMDAR antagonist, has quick and significant antidepressant effects within hours. Because of its rapid antidepressant effects, research on ketamine has continued to uncover its mechanisms of action and identify new therapeutic targets. Ketamine raises prefrontal cortex BDNF, especially in the hippocampus, making it antidepressant-like. Scientific research has demonstrated that ketamine can enhance synaptic protein synthesis via BDNF signalling pathways that rely on the AKT and mTORC1 signalling cascades. Ketamine can modulate the phosphorylation of glycogen synthase kinase (GSK)-3β, activate mTOR through the upstream enzyme AKT, and have antidepressant effects. Ketamine has the potential to repair synaptic abnormalities caused by chronic stress, enhance synaptic function through homeostatic processes, and block NMDARs in postsynaptic main neurones in the prefrontal cortex and hippocampus (Figure 2).

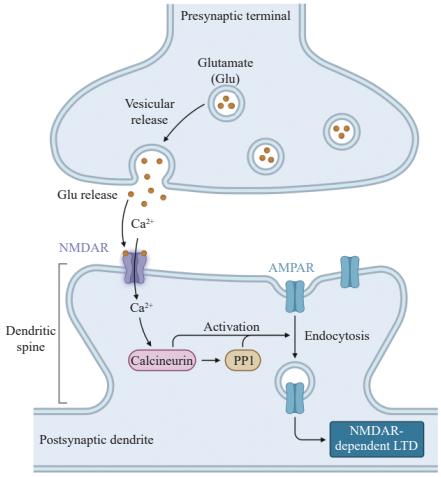

Figure 2 Pathway for NMDARs dependent long-term depression

AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor. PP1, protein phosphatase 1. LTD, long-term potentiation

6 Phytochemicals against depression

Herb phytochemicals may reduce the risk of autoimmune, cardiovascular, and neurological illnesses. Many polyphenols possess antioxidant and anti-inflammatory properties, including curcumin, ferulic acid, proanthocyanidin, quercetin, and resveratrol [41, 42]. Multiple studies indicate that these phytochemicals possess neuroprotective benefits, suggesting they may alleviate symptoms of depression. However, the effectiveness of these compounds can vary significantly among individuals due to differences in absorption, metabolism, and genetic factors [43]. To address these challenges, digital health technologies can play a crucial role in optimising the use of these phytochemicals. Mobile health applications (apps) equipped with mood-tracking features allow patients to self-report various symptoms, such as mood fluctuations, anxiety levels, sleep quality, and energy levels. These apps can use data analytics to assess the impact of herbal supplements in real-time, allowing for timely adjustments to dosages or herbal combinations. Wearable devices that monitor physiological markers, such as heart rate variability, skin temperature, and sleep patterns, can provide objective data on how patients respond to herbal treatments. An increase in heart rate variability, for example, might indicate enhanced stress

resilience after consuming adaptogenic herbs like *Rhodiola rosea*. Telehealth platforms can facilitate regular check-ins with healthcare providers, enabling continuous monitoring of patients using herbal therapies. This approach ensures adherence to treatment protocols and minimises potential side effects.

6.1 Resveratrol

Resveratrol is a naturally occurring phenol resveratrol. Resveratrol was detected in cerebral fluid during a clinical trial in which participants were administered 500 mg orally for 13 weeks [44]. Resveratrol is primarily glucuronidated and sulfated in the liver, which reduces its bioavailability to approximately 0.5% even though it is absorbed at a 70% rate when taken orally [45]. Buccal delivery, which is absorbed directly via tissues inside the mouth, could offer a solution to this issue. After one minute of keeping a 50/50 alcohol/water solution containing 1 mg of resveratrol in the mouth, plasma levels of the compound reached 37 ng/mL. Taking 250 mg of resveratrol as a tablet could achieve this concentration [46]. Several investigations have demonstrated its neuroprotective and anti-inflammatory effects [47]. Resveratrol has been reported to reduce 5-HT/noradrenaline absorption and decrease the activity of monoamine oxidase (MAO) in animal models. Additionally, trans-resveratrol (20 – 80 mg/kg) has demonstrated antidepressant effects by boosting 5-HT and noradrenaline levels in the brain. This phytochemical has also been shown to prevent behaviors associated with depression induced by chronic stress, potentially through the modulation of neurotransmitter levels such as 5-HT, dopamine, and noradrenaline, which leads to decreased MAO activity [48, 49].

6.2 Proanthocyanidins

Plants such as apples, cocoa beans, grapes, and tea contain proanthocyanidins, which are flavan-3-ols that can be either oligomeric or polymeric. Numerous pharmacological actions, including cardioprotective, antioxidant, and antinociceptive effects, have been demonstrated by researchers in relation to these phytochemicals [50]. ASENSI et al. [51] found that administering oral proanthocyanidin at 25 and 50 mg/kg for 7 d reduces immobility time in mice during forced swimming and tail suspension tests. After the injection of proanthocyanidins, the concentrations of 5-HT in the hypothalamus, hippocampus, and prefrontal cortex increased. Proanthocyanidin's antidepressant effects may involve central monoaminergic neurotransmitters.

6.3 Quercetin

The polyphenolic flavonoid quercetin is present in a wide variety of plant and pharmaceutical foods. Reportedly, this flavonol scavenges free radicals (the culprits behind oxidative chain reactions), and therefore inhibits the oxidation of other molecules [52]. Although quercetin does not target any protein kinase enzymes, it does activate oestrogen receptors [53]. Mice hyperactivated along the hypothalamic-pituitary-adrenal (HPA) axis exhibited depressive-like behaviours, which quercetin (20 – 40 mg/kg) avoided in preclinical investigations. When administered intravenously (10 – 20 mg/kg) of fluoxetine, the impact was similar [54].

6.4 Carvacrol

Isolated from aromatic herbs like thyme and oregano, carvacrol is a monoterpenic phenol. This fragrant plant compound has a wide range of beneficial effects, including reducing inflammation, alleviating pain, easing arthritis, warding off allergies, preventing cancer, lowering blood sugar, and protecting the heart, intestines, liver, and nervous system [55]. This phenolic monoterpene regulates the activity of the human ion channels transient receptor potential vanilloid 3 (TRPV3) and A1, which subsequently generates thermal sensations [56]. Additionally, carvacrol has been found to activate Peroxisome proliferator-activated receptor (PPAR) and inhibit inflammation mediated by cyclooxy genase-2 (COX-2) [57]. It is crucial to exercise caution when administering carvacrol alongside other compounds mostly metabolised by cytochrome P4502A6 (CYP2A6) [58]. CYP2A6 is the most important drug-metabolising enzyme involved in carvacrol metabolism. Oral administration of carvacrol (12.5 – 50 mg/kg) appears to alleviate depression in rats through dopaminergic brain circuits [59]. FRIEDMAN et al. [60] found that carvacrol (12.5 mg/kg, 7 d) increases 5-HT and dopamine levels in the prefrontal cortex and hippocampus.

6.5 L-theanine

The amino acid L-theanine was discovered in 1949 in *Camellia sinensis* or green tea. This amino acid improves anticancer activity, prevents vascular disorders, lowers blood pressure, fights obesity, boosts the immune system, and protects the brain [61]. Because it is chemically linked to glutamate, an excitatory neurotransmitter, and binds to glutamate receptors with a lower affinity, it affects behaviour [62]. It binds to NMDARS and agonists them while opposing AMPAR. In the central nervous system (CNS), L-theanine suppresses glutamate reuptake and enhances γ-aminobutyric acid, dopamine, and serotonin [63]. L-theanine can exert a modest anxiolytic effect by increasing the activity of γ-aminobutyric acid, the primary inhibitory transmitter in the brain. The impact of L-theanine on the attentional process was shown that continuous processes affected by L-theanine are

responsible for sustaining focus throughout challenging tasks, as opposed to processes specific to moment-to-moment phases [64].

6.6 Curcumin

Curcuma longa is a significant source of the active ingredient because of curcumin. Ongoing research is being conducted on the potential medical effects of this naturally occurring yellow phenol, which has a long history of usage in oriental medicine [65]. Low tissue and plasma levels, fast metabolism, and swift excretion were observed following oral doses of curcumin [66]. Due to its insolubility in water and poor absorption, the bioavailability of curcumin is being improved in several ways. Examples include absorption factors, structural mimics, liposomes, and nanomaterials [67]. Several mice models have shown that curcumin supplements can alleviate symptoms of depression. To improve step-down passive avoidance and open-field behaviour, rats received 1.25 – 10 mg/kg curcumin orally for 14 d. Curcumin reduced immobility in the forced swimming test and completely corrected bilateral olfactory bulbectomy-induced changes of 5-HT, noradrenaline, and dopamine levels in the hippocampus [68].

6.7 Ferulic acid

Ferulic acid is an antioxidant [69]. This molecule possesses anti-inflammatory, anti-tumour, antidiabetic, and neuroprotective properties. From phenylalanine, 4-hydroxycinnamic acid and caffeic acid are produced. YABE et al. [70] found that oral ferulic acid at 100 and 250 mg/kg reduced stress-induced abnormal behaviour in depression model mice. They also found that ferulic acid increases brain-derived neurotropic factor mRNA and CREB phosphorylation in the hippocampus.

7 Medical herbs against depression

One of the most common forms of alternative medicine is herbal treatment [71]. Herbal remedies are a common first line of defence against depression, and supplementary and alternative medicine is always an option for those suffering from the disorder [72]. Both animal studies and human clinical trials have shown that several medicinal plants can alleviate symptoms of depression (Table 1). These antidepressant herbs have psychopharmacological effects through modulating neuroendocrine pathways, inhibiting MAO, and regulating 5-HT/dopamine/noradrenaline reuptake.

7.1 *Bridelia retusa*

The *Bridelia retusa* plant, a member of the Euphorbiaceae family and often called as asan or arghan, can be found up to a thousand meters in elevation, except for extremely arid regions. *Bridelia retusa* is a plant native to warmer regions of India; its entire plant is used in traditional medicine to treat various illnesses. Traditional users of this plant's bark have reported success in treating rheumatism, viruses, snake bites, and infertility. The multiple phytochemicals found in the plant's leaves, bark, roots, and fruit include steroids, tannins, phenols, flavonoids, and saponins. The antifungal and antibacterial properties of the isoflavone found in the leaves lend credence to their usage in ayurvedic treatments for wounds and urinary tract infections (UTIs). Isolated from leaves, chitosan flavonoid exhibited analgesic and anti-inflammatory effects.

7.2 *Camellia sinensis* (green tea)

Green tea is made from the leaves of the *Camellia sinensis* plant. Among green tea's many health benefits include its ability to fight cancer, fibrosis, inflammation, and neurological diseases [83]. *Camellia sinensis* polyphenols ameliorated depressive symptoms and lowered corticosterone levels in recent preclinical research. These findings point to the possibility that polyphenols found in green tea can control the HPA axis, which plays a role in the pathophysiology of depression [84].

7.3 *Lavandula angustifolia* (Lavender)

The scented medicinal plant known as *Lavandula angustifolia* originates from regions that stretch from Spain and France to Italy. A normal measurement for its height is half a metre to one metre. The leaves have a decussate pattern and are hairy and lanceolate. The blooms are symmetrical, have a violet to violet-blue colour, and have the typical shape of the Lamiaceae family: petals that fuse into an upper and lower lip. Clusters of six to ten flowers bloom at the very top of a stem.

According to the European medicines agency monograph on lavender, the herbal material used for the following indications is lavender flowers: alleviation of mild symptoms of mental tension and fatigue and promoting sleep [85, 86]. Traditional use is the basis for these approved therapeutic indications. You can make a tincture and essential oil from steam-distilled lavender flowers or drink the tea straight from the flower. As an additional usage, essential oil can be added to bath water [87, 88]. The antibacterial, spasmolytic, and oestrogenic effects of lavender oil have been studied *in vitro*. There have been observations of sedative, anti-inflammatory, analgesic, and anticonvulsive effects in rats and mice when tested *in vivo*. Results may not be generalisable to human subjects at clinically significant doses because of the large dosages employed in these trials.

The effectiveness of oral lavender oil in alleviating symptoms of generalized anxiety disorder (GAD) and

Table 1 Phytochemicals, molecular mechanisms, and clinical outcomes for MDD

Phytochemical	Source	Molecular mechanism	Clinical outcome	Reference
Curcumin	*Curcuma longa*	Anti-inflammatory via NF-κB inhibition, enhancing BDNF expression, and antioxidant by scavenging ROS	Improved mood and cognitive function in clinical trials, and reduced symptoms of MDD after 4 – 8 weeks of use	[73]
Saffron	*Crocus sativus*	Modulates serotonin reuptake, and antioxidant and anti-inflammatory effects	Comparable efficacy to SSRIs (e.g., fluoxetine) in mild to moderate MDD, and reduced Hamiton Depression Rating Scale (HDRS) scores	[74]
Rhodiola rosea	Adaptogenic herb	Enhances serotonin and dopamine levels, and modulates HPA axis activity	Improved resilience to stress and reduced depression symptoms in mild to moderate cases	[75]
Hypericum perforatum	St. John's Wort	Inhibits serotonin, norepinephrine, and dopamine reuptake, and downregulates HPA axis hyperactivity	Effective for mild to moderate MDD, and comparable efficacy to conventional antidepressants with fewer side effects	[76]
Proanthocyanidins	Grape seeds, cocoa	Modulating monoaminergic neurotransmission, and antioxidant and anti-inflammatory effects	Improved mood in preclinical studies, and shown to enhance serotonin and norepinephrine levels	[77]
Quercetin	Various fruits/plants	Reduces HPA axis hyperactivity, scavenges free radicals, and inhibits oxidative stress	Preclinical studies show reduced depressive-like behaviours in animal models	[78]
Carvacrol	Thyme, oregano	Modulating dopaminergic pathways, and anti-inflammatory via COX-2 inhibition	Preclinical studies demonstrate antidepressant-like effects by increasing dopamine levels	[79]
L-theanine	Green tea (*Camellia sinensis*)	Enhances GABA, dopamine, and serotonin, and modulates glutamate activity at NMDARs	Reduced anxiety and improved mood, and shown to enhance cognitive focus and relaxation	[80]
Resveratrol	Grapes, red wine	Inhibits MAO activity, and enhances serotonin, dopamine, and norepinephrine levels	Reduced depressive behaviours in preclinical studies, and neuroprotective effects observed in clinical trials	[81]
Ferulic acid	Grains, fruits	Enhances BDNF expression, and reduces oxidative stress and neuroinflammation	Preclinical studies show improved neurogenesis and reduced depressive-like behaviors	[82]

mixed depression and anxiety has only been demonstrated in a small number of randomised clinical trials. There were 539 participants in a clinical trial for GAD. The trial was randomised and double-blind. After 10 weeks, subjects were given either paroxetine, a preparation of lavender oil, or a placebo. Lavender oil reduced Hamilton anxiety scale ratings by more than 50% in 60% of patients, and side events were equivalent to the placebo group. A similar study examined the efficacy of lavender oil for anxiety and insomniacs. Unlike the control group's 33.3% response rate, 48.8% of experimental patients improved after therapy. In a placebo-controlled trial, mixed anxiety and depression patients did better in the placebo group than in the lavender oil group.

7.4 *Nelumbo nucifera*

Long ago, ancient Asians used *Nelumbo nucifera* fruit (*Nelumbinis semen*) to soothe them. Our group and colleagues discovered emotional benefits and depression treatment mechanisms. In rat models of depression, nelumbinis semen restored 5-HT1AR affinity and antidepressant effects [89]. Funnily enough, it worked better than *Hypericum perforatum*, the most popular natural antidepressant [90]. The forced swimming test showed that Nelumbinis semen reduced chronic moderate stress-induced visiting counts and increased start delay, rearing number, and grooming time. No treatment-related toxicity associated with Nelumbinis semen was seen in rats after 13 weeks of therapy and in dogs after 28 d of administration [91].

7.5 *Rhodiola rosea* (rose root)

Some Asian and European countries have utilised the biennial blooming plant *Rhodiola rosea* as a traditional remedy. Aphrodisiac and nootropic properties have been associated with *Rhodiola rosea* [92]. *Rhodiola rosea* extract (1.5 – 6 g/kg) raised rat hippocampal 5-HT levels in a depression study. *Rhodiola rosea* extract rejuvenated hippocampal neuronal cells by stimulating neural stem cell growth [93]. MATTHIOLI et al. [94] showed that *Rhodiola rosea* extract (10 – 20 mg/kg, 3 weeks) is an antidepressant in rats using behavioural tests. Chronic *Rhodiola rosea* extract treatment inhibited mild stress-induced behavioural and physiological alterations. VAN DIERMEN et al. [95] found that MAO inhibition causes *Rhodiola rosea*'s antidepressant effect. Phase III clinical trials using *Rhodiola rosea* extract (340 – 680 mg/d) for mild to severe depression revealed considerable improvement compared to the placebo group (randomised, double-blind, and placebo-controlled experiment) [96].

7.6 *Piper methysticum* (Kava)

Kava, a hallucinogenic drink made from *Piper methysticum* roots, has a long history in the South Pacific. Many countries, including the US and Europe, employ its extract to treat anxiety [84]. *Piper methysticum* extract was tested for anxiolytic and depressive properties in a 2009 3-week double-blind crossover trial with 60 participants. According to the Montgomery-Asberg Depression Rating Scale (MADRS), consuming 16 g of *Piper methysticum* aqueous extract daily—which contains 250 mg of kavalactones, improves comorbid depression. No significant side effects or clinical hepatotoxicity were identified in the extract, supporting its safety as a medicine [97]. Some manufacturers pulled this therapeutic herb due to latent hepatotoxicity [98].

7.7 *Hypericum perforatum*

The plant *Hypericum perforatum* is famous for treating depression [99]. Multiple clinical investigations have demonstrated *Hypericum perforatum* treats depression [100]. A long-term follow-up study involved 426 subjects who received *Hypericum perforatum* extract (900 mg/d) to determine remission rates. *Hypericum perforatum* extract was found to be effective in preventing recurrence following acute depression recovery, as well as being as tolerable and maintenance-friendly as a placebo in the long run. *Hypericum perforatum* extract has the same therapeutic effects as conventional antidepressants with fewer side effects [101]. It is also superior to placebo in treating depression. Recent findings suggest that *Hypericum perforatum* interacts with several drugs, which could cause significant side effects [102]. Phenprocoumon, digoxin, warfarin, human immunodeficiency virus (HIV) protease inhibitors, cyclosporin, theophylline, and oral contraceptives have certain clinically relevant interactions that reduce their concentration or impact. Plant constituent may induce cytochrome metabolising enzymes and P-glycoprotein, causing these interactions.

7.8 *Crocus sativus* (Saffron)

Saffron comes from the flowering plant *Crocus sativus*. Saffron (30 mg/d) improved the HDRS scores compared with placebo in two randomised controlled trials [103]. Three randomised controlled trials comparing saffron to imipramine or fluoxetine demonstrated equivalent HDRS effects [104]. One review revealed that Saffron supplementation helps mild to severe depression, while a small meta-analysis found that it relieves symptoms [105]. The authors credit Saffron's antidepressant effects to its antioxidant, anti-inflammatory, and neuroprotective qualities. A recent randomised, placebo-controlled research by MAZIDI et al. [106] found that saffron (100 mg/d, 12 weeks) alleviated depressive symptoms with few side effects.

7.9 *Valeriana officinalis* (Valerian)

The Caprifoliaceae family includes the Valerian plant, whose scientific name is *Valeriana officinalis*. Traditional medicine makes frequent use of this plant's roots, and it also has a lovely aroma. Valerian root is used in Iranian medicine as an analgesic, food digester, anticonvulsant, hypnotic, depressant, and anti-colic. Valerian has been shown to treat depression in animals. However, little clinical research has examined the plant's antidepressant properties. MÜLLER et al. [107] tested valerian and *Hypericum perforatum* as antidepressants in 2 500 mild-to-moderate depressed patients.

7.10 *Chamaemelum nobile*/*Matricaria recutita* (chamomile)

Even in ancient times, the dried flowers of the chamomile plant were recognised as a potent herbal remedy. Chamomile has a long history of usage in the traditional medicine of these nations for a variety of purposes, including pain relief, gastrointestinal issues, and wound healing. Although chamomile comes in a variety of forms, the two most common are the *Chamaemelum nobile* and *Matricaria recutita*. Animal studies and human trials on depression both demonstrated that German chamomile alleviated symptoms. AMSTERDAM et al. [108] conducted double-blind clinical research where 57 patients with mixed anxiety and depressive disorder (MADD) were provided with either a placebo or chamomile capsules at a dosage of 220 mg/d for eight weeks. Our sample includes 19 MADD patients, 16 with anxiety disorder and a history of depression, and 22 with anxiety condition but no history of depression. After eight weeks of treatment, chamomile significantly reduced depression compared with placebo. Furthermore, chamomile had a stronger effect on people with MADD compared with non-MADD patients.

7.11 *Ginkgo biloba* (Maidenhair tree)

As a big deciduous tree with fan-shaped leaves, the Maidenhair tree is a member of the family Ginkgoceae. Originally from China, Japan, and Korea, this tree is currently cultivated all around the globe. A wide range of illnesses have been traditionally treated with the plant's seeds and leaves according to traditional Chinese medicine. According to pharmacological research, the plant's leaf extract may widen arterial arteries, increasing blood circulation and perfusion to the tissues. Memory and intelligence are both boosted by the herb's leaf extract, which raises blood flow to the brain. In both the US and Germany, *Ginkgo biloba* is currently among the most sought-after herbs. *Ginkgo biloba* extract is given for age-related mental and physical diseases in these nations under the names of Tanakan and Rokan [109]. Iran markets *Ginkgo*

biloba as a memory booster [110]. Twenty-seven seasonal affective disorder patients received ten weeks of *Ginkgo biloba* or placebo in double-blind clinical research. The study found no statistically significant change in depression levels between groups, possibly due to the small sample size [111]. Research showed that major depressed individuals who took trimipramine (200 mg) and *Ginkgo biloba* extract (240 mg/d) improved their sleep [112]. Patients with significant depression who experience sexual dysfunctions because of antidepressants find relief with the help of *Ginkgo biloba* extract.

7.12 *Echium amoenum*

Iranian Echium, formally known as *Echium amoenum*, is a member of the Boraginaceae family that is native only to Iran's Alborz Mountain Range. Iranians have long relied on this herb for its calming and mood-boosting properties. Clinical trials have demonstrated that *Echium amoenum* has anxiolytic and depressive properties [113]. For 6 weeks, 35 participants in a randomised controlled experiment were given either a placebo or *Echium amoenum* (375 mg/d) for moderate to mild depression. The *Echium amoenum* group showed a marked improvement in depressive symptoms after 4 weeks. Compared with the placebo, the adverse effects of *Echium amoenum* were not statistically different. Table 2 shows studies reported on the antidepressant efficacy of medicinal plants.

8 Novel treatment therapeutics

A significant incidence of relapse and a slow onset are hallmarks of MDD [133]. Individuals at high risk of MDD should undergo psychiatric therapies, according to the American Medical Association. Interpersonal therapy, Cognitive behavioural therapy (CBT), acceptance and commitment therapy, psychodynamic therapy, and cognitive therapy are among the most popular strategies utilised to treat depression [134]. In particular, relapse risk is significantly reduced in MDD cases when

Table 2 Studies reported on the antidepressant efficacy of medicinal plants

Plant	Plant used	Subject	Assessment	Type of study	Finding	Reference
Hypericum perforatum	Fluoxetine with *Hypericum perforatum* extract (800 mg)	149 participants who were 65 and older, and suffering from mild to moderate depression	HDRS	Trial that was both randomised and double-blind	The antidepressant effects of *Hypericum perforatum* extract were comparable to those of fluoxetine	[114]
	Treatment for 6 weeks with WS® 5570 (600 or 1 200 mg/d) or a placebo	332 persons afflicted with moderate to mild depression	HDRS	Clinical trial using a placebo group that was randomised and double-blind	In comparison with placebo, WS® 5570 (600 or 1 200 mg) demonstrated a notable antidepressant effect	[115]
	Treatment for 6 weeks with WS5573 (300 mg containing 0.5% or 5% *Hypericum perforatum*) or a placebo	147 individuals exhibiting mild to moderate depression	HDRS	Not mentioned	WS5572 (5% *Hypericum perforatum*) demonstrated a notable antidepressant impact when contrasted with a placebo	[116]
	Combined with imipramine or a placebo, 1 050 mg of *Hypericum perforatum* extract three times a day	263 individuals depressed to a moderate degree	Medical worldwide impressions scale, HDRS	Phase III randomised controlled trial with multiple centres and parallel groups	The efficacy of *Hypericum perforatum* extract was comparable to that of imipramine, and it was even more effective than the placebo	[117]
Crocus Sativus	One Saffron capsule (30 mg daily) or a placebo during two menstrual periods	People who experience menstruation irregularities	HDRS	Randomised, placebo-controlled experiment with two sets of participants	In comparison with placebo, extract had a statistically significant antidepressant effect	[118]
	30 mg of Saffron extract and 60 weeks of fluoxetine	40 individuals suffering from moderate to mild depression	HDRS	Randomised, controlled study	In terms of efficacy, the extract was on par with fluoxetine	[119]
	Saffron (30 mg) and imipramine (60 mg) for 6 weeks	30 people suffering from severe depression	HDRS	Not mentioned	Comparable to imipramine, the extract had an impact	[120]

Table 2 Continued

Plant	Plant used	Subject	Assessment	Type of study	Finding	Reference
Rhodiola rosea	6 weeks of extract (340 or 640 mg) or placebo	89 psychiatric patients ranging from moderate to severe	HDRS and the Beck Inventory	Randomised, double-blind, placebo-controlled	The antidepressant impact was significantly stronger at both doses when compared with the placebo	[96]
	For 12 weeks, take 300 mg of extract with sertraline	57 people suffering from severe depression	Beck Depression Inventory, HDRS change in clinical global impression, inventory scale	Randomised, double-blind, placebo-controlled	Although extract had less side effects, it was less effective than sertraline	[121]
Curcumin (*Curcuma longa*)	For 6 weeks, take 1 000 mg of curcumin with 500 mg of fluoxetine	60 major depressive disorder patients	HDRS	Trial using observational masks	The combination of curcumin and fluoxetine was more effective than either drug alone	[122]
	8 weeks of a 500 mg curcumin/placebo regimen	56 individuals diagnosed with severe depression	Psychological Assessment of Major Depressive Disorder, Spielberger State-Trait Anxiety Subscale	Randomised, double-blind, placebo-controlled	When compared with placebo, curcumin demonstrated a statistically significant antidepressant effect	[123]
	One year of placebo or curcumin (500 mg/d)	40 individuals suffering from severe depression	Scales for Clinical Global Impression and Severity, HDRS, and MADRS	Not mentioned	Comparable to imipramine, citalopram, and venlafaxine, the extract demonstrated efficacy	[124]
Ginkgo biloba	2 weeks of electrocon vulsive therapy (ECT) with extract (40 mg every 8 h) or placebo	81 people suffering from severe depression	HDRS	Clinical trial using a placebo group that was randomised and double-blind	Extract outperformed placebo in terms of effectiveness	[125]
	Ginkgo biloba tablets or placebo for 10 weeks	27 individuals diagnosed with seasonal affective disorder	MADRS	Randomised study	The onset of winter depression symptoms could still be triggered by the extract	[126]
Chamomile	8 weeks of 220 mg/d placebo/ chamomile pills	57 individuals diagnosed with a depressive and anxious disorder	HDRS	Research that was randomised, double-blind, and controlled with a placebo	The extract had a far stronger impact than the placebo	[108]
	Taking a placebo or chamomile tea for 15 d	80 postnatal women	Empirical Measure of Postpartum Depression	Randomised controlled trial including pre- and post-tests	The effects of tea were significantly greater than those of the placebo	[127]
Valeriana officinalis	Take 600 mg of 100 mg of Valerian, or both at once	40 patients with a first episode of depression participated in a 5-week, double-blind, randomized, placebo-controlled study	HDRS	Clinical trial	Better benefits were observed when plants were combined	[128]
Lavandula angustifolia	3% aromatherapy with lavender	17 hospice patients with cancer	Evaluation tool for verbal analogues	Clinical trial	Aromatherapy outperformed the control group significantly	[129]
	The dosage of 5 mg of lavender taken twice a day in addition to 20 mg/d of citalopram taken for 8 weeks	80 people suffering from moderate to mild depression	HDRS	Randomised clinical study	The case group exhibited substantially fewer signs of depression	[130]

Table 2 Continued

Plant	Plant used	Subject	Assessment	Type of study	Finding	Reference
Lavandula angustifolia	Using a combination of 60 drops of Lavender oil and 100 mg of imipramine or a placebo for 4 weeks	45 people suffering from moderate to mild depression	HDRS	Conducting a randomised, double-blind experiment	The effect of lavender alone was less than that of imipramine	[131]
Echium amoenum	6 weeks of placebo/Echium (375 mg/d)	35 individuals suffering from moderate to mild depression	HDRS	Randomised controlled trial	There was no discernible difference between the echium and the placebo	[132]

antidepressants and psychological therapies are used together [135]. Alternative methods of therapy are available. Patients with MDD can benefit from the clinical application of repetitive transcranial magnetic stimulation (rTMS). Results from several studies have demonstrated that rTMS is a successful treatment for MDD in a wide range of age groups, including younger patients, adults, and those in their 80 s and 90 s. There is some evidence that older people suffering from depression may have better outcomes if they begin using rTMS sooner rather than later [136]. Additionally, studies have shown that rTMS is an effective treatment for postpartum depression [137]. There is mounting evidence that rTMS to the left dlPFC's anterior stimulation site can improve treatment results.

Phototherapy also has powerful and quick effects on mood and attentiveness, which plays an important role in controlling emotional behavior [138]. The treatment efficacy of phototherapy for MDD is supported by more evidence [139]. The efficacy of antidepressants is enhanced when used in conjunction with phototherapy. To influence the synthesis of 5-HT and hormones in the brain, phototherapy makes use of intense light of a particular wavelength to excite the retina [140]. Another possible explanation for how phototherapy reduces MDD symptoms is that it acts by focusing on a circuit that includes the intergeniculate leaflet, retinal-thalamic ventral lateral geniculate nucleus, and lateral habenula. In this regard, acupuncture's efficacy in MDD has been encouraging. A variety of illnesses can be alleviated with this ancient Chinese therapeutic method, which mostly comprises traditional body needling, moxibustion, electroacupuncture, and laser acupuncture [141]. There are fewer adverse effects and lower costs associated with acupuncture than pharmaceutical treatments. While it is known that electroacupuncture (EA) stimulation can successfully cure MDD, the exact process by which acupuncture alleviates depression is still not fully understood. Prior studies demonstrated that applying EA at the Zusanli (ST36) acupoint might ameliorate depressive-like behaviour and stop the reduction of prefrontal cortical astrocytes in mice exposed to chronic unpredictable mild stress (CUMS). It is hypothesised that acupuncture at the Baihui (GV20) and Shenting (GV24) acupoints may regulate the CaMK signalling pathway, which in turn alleviates symptoms of depression. There may be a correlation between EA's antidepressant effects and enhanced synaptic transmission in the ventromedial prefrontal cortex (vmPFC) [142].

Mostly herbal supplements, along with emerging digital therapeutics, are increasingly more widespread use in enhancing treatment results [143, 144]. Among these digital interventions, VR therapy, digital CBT, and neuromodulation techniques will be synergised with the effects of phytomedicines. Specifically, digital cognitive behavioral therapy (CBT) programs, available through websites or mobile apps, can efficiently reduce symptomatology in depression. Taking this medication with herbal supplements, including *Hypericum perforatum* or Saffron, might help the patients enjoy better conditions faster and with the positive effects of the medication's mood stimulation.

Applications such as virtual reality platforms can simulate calming environments that reduce levels of anxiety and stress, which are highly prevalent in patients with MDD. This can be combined with herbs with anxiolytic properties, such as lavender, to enhance reinforcement of relaxation and mood improvements. Digital biofeedback tools, in other words, measuring and giving feedback regarding physiological responses of heart rate or muscle tension, can further fuel the effects of herbal anxiolytics, such as valerian or chamomile root. They can be better masters over their stress responses and thus more efficiently strengthen the therapeutic potency of the herbs.

Digital health technologies are revolutionising how traditional treatments, such as phytotherapy, are monitored, optimised, and personalised for conditions like MDD. By leveraging advancements in wearable sensors, AI-driven analytics, and telehealth platforms, digital tools can enhance the efficacy of herbal treatments in ways previously unattainable. These mechanisms allow real-time monitoring of physiological responses, precision in treatment delivery, and feedback loops that integrate patient-specific data to optimise outcomes.

Wearable devices, such as fitness trackers or specialised health monitors, can continuously track physiological markers like heart rate variability (HRV), a sign of reduced stress, skin temperature, and sleep patterns. For instance, Adaptogenic herbs like *Rhodiola rosea* have improved stress resilience. Using wearable devices,

researchers can correlate increased HRV with the intake of Rhodiola, enabling precise adjustments to dosage or timing based on the patient's response [145]. In a study by IQBAL et al. [146], wearable sensors were used to monitor the effects of adaptogenic herbs on stress markers in patients. Results indicated measurable improvements in HRV and reduced cortisol levels in patients in conjunction with guided biofeedback, demonstrating the synergy between herbal treatments and digital tools. To tailor phytotherapy treatments, AI algorithms can analyse large datasets, including patient genetic profiles, metabolic markers, and behavioural data. This approach ensures the right herb, dosage, and combination are prescribed for individual needs. SAADATI et al. [21] demonstrated the efficacy of AI in optimising treatment protocols by integrating genomic data with patient-reported symptoms [147]. Patients receiving AI-tailored curcumin doses experienced fewer side effects and faster symptom alleviation than standard dosing approaches.

Virtual reality platforms provide immersive calming environments that enhance the anxiolytic and mood-stabilising effects of certain herbs. VR simulations can be used as adjunct therapies, amplifying the psychological benefits of phytomedicines. A randomised controlled trial by AMITANI et al. [148] found that patients undergoing VR-based relaxation therapy while using lavender oil exhibited a 30% greater reduction in depression and anxiety symptoms compared to standard care groups. Mobile health (mHealth) apps enable patients to log symptoms such as mood, sleep quality, and energy levels, providing a dynamic feedback loop for healthcare providers. These apps can analyse trends and recommend adjustments to phytotherapy treatments. A study integrating an mHealth app demonstrated improved adherence and outcomes. The app provided reminders and collected user feedback, helping clinicians adjust treatments based on user-reported mood improvements [149].

9 Neuromodulation therapy

Neuromodulation therapy uses micro-current, magnetic pulse, or neural feedback technologies to regulate central or peripheral nervous system excitatory/inhibitory activity within the therapeutic dose to reduce disease symptoms. ECT is one of the most effective depression treatments due to safer equipment and approaches such as modified ECT [150]. Recent RCTs and meta-analyses demonstrate that rTMS is safe for depression treatment [151]. Light therapy, deep brain stimulation, vagal nerve stimulation, and transcranial alternating current stimulation (tACS) are some of the newer, more promising depression treatments [152-154]. Still, some have not been widely implemented due to their experimental nature. Insufficient data support tACS for depression treatment, but tACS has less sensory experience and unpleasant reactions with modest electrical current in a sine-wave pattern than transcranial direct current stimulation (tDCS). Recently, ALEXANDER et al. [155] found that sham, 10-Hz, and 40-Hz tACS were similarly effective. The 10-Hz tACS group responded more than the sham and 40-Hz groups at week 2. The effectiveness of tACS needs to be confirmed by other RCT studies. Further research is also required to determine how neuromodulation therapy alleviates depression.

10 Precision medicine for depression

Improving the therapeutic effects of depression can be achieved by optimising the therapy strategy. Nonetheless, responses to depression therapy might vary significantly from one patient to another. Consequently, this raises the issue of tailored treatment, specifically regarding which treatments are appropriate for different patients.

One of the significant barriers in treating MDD is the heterogeneity of patient responses to pharmaceutical and herbal treatments. Precision medicine, supported by digital health technologies, now brings possibilities in treatment tailoring based on individual genetic, physiological, and behavioural profiles. Genomic analysis can identify genetic markers that predict a patient's response to herbal therapies. For instance, curcumin modulates inflammation pathways more effectively than other actions that may leverage patient genetic variations. The digital systems can collect data integrated into the biomarkers, which correlate with treatment algorithms. This process aids in determining the most effective herbal remedy a clinician can apply. It will sift through vast amounts of data gathered from patients' health records, wearable devices, and genetic profiles to predict which herbal treatments best suit a patient. It will allow customised treatment plans that continuously adapt based on the patient's input and real-time data. digital health platforms can assimilate information from wearable sensors, mHealth apps, and genetic data with the ability to offer special herbs and dosages. For instance, if the patient is not responding to saffron supplements, the system shall also advise other alternatives, such as Rhodiola or *Hypericum perforatum*, depending on the patient's genetic profile and symptoms.

Peripheral protein expression, genetics, neuroimaging, electrophysiology, developmental trauma, neurocognitive performance, personality, and antidepressants and psychotherapies have all been areas of interest for psychiatrists and psychologists in the last ten years when trying to predict treatment efficacy [156]. For instance, a 12-week RCT by YUE et al. [157] found that pharmacogenetic guidance patients had a much better response and remission rate than non-pharmacogenetic guidance patients.

Afterwards, GREDEN et al. [158] performed an 8-week randomised controlled trial of genomics to improve depression decisions (GUIDED) on 1 167 MDD patients.

While both groups showed no difference in symptom improvement, the pharmacogenomics-guided group had a much higher response rate and remission rate. Cognitive behavioural therapy, pharmaceuticals, ECT, rTMS, and transcutaneous vagus nerve stimulation are all potential treatments for major depressive disorder, according to a recent meta-analysis [159]. Nevertheless, there is still a great deal of unfinished business regarding the clinical application of biomarkers that forecast therapy response on an individual level (Table 3).

Table 3 Drugs under clinical trials for CNS depression activity

Drug name	Trial title	Phase	Status	Condition	Key outcome	Reference
Diazepam	Efficacy of diazepam in CNS depression patients	Phase 2	Completed	Anxiety disorders	Reduction in CNS depressive symptoms	[160]
Clonazepam	Clonazepam and CNS depression in epilepsy	Phase 3	Recruiting	Epilepsy, CNS depression	Safety and efficacy in reducing CNS depression	[161]
Propofol	Propofol for CNS depression in anesthesia	Phase 4	Active, not recruiting	Anesthesia, CNS depression	Optimal dosage and patient recovery rates	[162]
Midazolam	Evaluation of midazolam in severe CNS depression	Phase 1	Completed	Severe anxiety, sedation	Effectiveness in controlling CNS depression symptoms	[163]
Phenobarbital	Barbiturate efficacy in treating CNS depression	Phase 2	Completed	Alcohol withdrawal syndrome	Symptom control and sedation rates	[164]
Ketamine	Ketamine's role in managing CNS depressive effects	Phase 3	Ongoing	Major depression, CNS depression	Improvement in depressive symptoms and functionality	[165]
Fentanyl	Fentanyl-induced CNS depression during surgery	Phase 4	Completed	Postoperative CNS depression	Post-surgical CNS depression control and patient safety	[166]
Lorazepam	Lorazepam for CNS depression in acute anxiety	Phase 2	Recruiting	Anxiety, CNS depression	Reduction in anxiety-induced CNS depressive states	[167]

mHealth apps are crucial for improving herbal treatment adherence by allowing patients to monitor their symptoms, like mood changes, anxiety, and sleep quality. Over time, the mHealth apps analyse these trends and provide actionable feedback regarding reminders for herbs or even adjusting timing suggestions [168]. Herbal remedies can be reached by telehealth to a greater extent. Reaching underserved populations becomes easy. Patients in rural or remote areas can get consultations from healthcare providers and discuss their herbal remedy-based progress. The provider will then advise combining the same with another herb, perhaps Valerian, or adjusting the dosage for effective results. These platforms bridge the accessibility gap while maintaining a very high standard of care.

This access, monitoring, and effectiveness of the practice have been improved by integrating digital health technologies, including telehealth and mHealth apps, into phytotherapy. For instance, a patient can now consult a phytotherapist or herbal medicine practitioner from anywhere due to removing geographical barriers through telehealth platforms. For example, one can use teleconsultation services in remote locations where traditional herbal therapy is more common but has fewer certified practitioners. A patient can now have the right phytotherapy program after a remote diagnosis and assessment of their symptoms, medical history, and lifestyle factors, thus assuring safe and effective usage of plant-based treatments.

Other mHealth apps are equally crucial in filling the gap between phytotherapy and digital health. For instance, "HerbList" and "PlantSnap" applications offer users full details on medicinal plants and their traditional uses, preparations, and contraindications. Other than the learning aspect, some applications aim to aid patient compliance in phytotherapy regimens. For instance, tracking symptoms and medication reminders through mHealth helps users monitor adherence to herbal prescriptions and record their activity. Information acquired through such apps can be transmitted to health care professionals to monitor and modify the course of treatment in real time.

For example, integrated applications could feature AI-driven diagnostics with suggested phytotherapy. Apps evaluate symptoms and data from wearables and return a list of evidence-supported herbal remedies. For instance, using input from heart rate variability and sleep quality through wearable devices, AI models may suggest Ashwagandha or Rhodiola to decrease stress. This combination of precision diagnostics with evidence-based phytotherapy promises a personalised and scalable approach to managing chronic conditions.

Telehealth has also enabled more research and education on phytotherapy. Through the telehealth platforms

in the clinical settings, there is implementation of phytotherapy for irritable bowel syndrome (IBS) and mild depression, among others. This has been made possible by having practitioners provide telemedicine consultations to patients, dietary advice, and herbal supplement prescriptions.

Integration of telehealth and mHealth with phytotherapy also enhances accessibility to treatment. This approach balances high technological integration of digital facilities into traditional medicinal practices that help introduce new options in the search for better access to healthcare, in most cases within areas less adequately represented by more conventional medical treatment facilities.

AI and wearable devices are gaining traction in precision medicine for depression, with several real-world cases highlighting their potential.

Practical applications in healthcare settings reveal promising outcomes. Remote monitoring programs have successfully utilised wearable data to adjust real-time treatment plans. Hospitals and clinics that integrated wearable devices with AI-powered platforms reported reduced hospitalisations and quicker diagnoses of depressive disorders.

Patient-centric success stories provide further evidence of the practical benefits of these innovations. One patient, for instance, avoided hospitalisation due to early AI alerts indicating worsening depression symptoms. These tools empower the patient to seek immediate care and adjust treatment under the guidance of their healthcare provider. Such cases highlight the real-world impact of wearable devices and AI in improving mental health outcomes and overall quality of life.

Despite these advancements, challenges remain, including false positives or negatives in wearable data and privacy concerns. In some cases, initial implementations faced resistance due to inaccuracies in AI models or difficulties in integrating wearable data into clinical workflows. However, subsequent iterations have addressed these limitations, improving the data's reliability and its acceptance by healthcare providers. These examples demonstrate that while challenges exist, the continued refinement of AI and wearable technologies holds immense promise for the future of precision medicine in depression treatment.

Synergy is furthered by virtual reality platforms that aid in forming a calming environment and thus augment the therapeutic impacts of herbs such as Lavender on anxiety. All these technologies make herbal treatments a precise, personalised, and data-driven solution for such complex conditions as depression and anxiety. Therefore, it becomes more efficient through this process using wearable devices, telehealth platforms, mHealth apps, and AI technologies to provide real-time monitoring, personalisation, and optimisation for herbal treatment. It fail to improve adherence and access alone but objectively validates the outcome of herbal therapy for evolution into a much more precise patient-centred therapy. The future development of phytotherapy moves into the digital world and offers scalable and practical solutions in the management of mental health disorders. Table 4 shows the advantages of digital health tools with herbal treatments vs. conventional methods.

Table 4 Advantages of digital health tools with herbal treatments vs. conventional methods

Category	Digital health + herbal treatment	Conventional method	Reference
Personalisation	AI-driven algorithms tailor treatments based on genetic, metabolic, and physiological data, ensuring individual optimisation	Standardised treatments are often "one-size-fits-all", leading to variable patient outcomes	[169]
Real-time monitoring	Wearable devices provide real-time data on biomarkers (e.g., HRV, sleep patterns, and cortisol), enabling prompt adjustments	Limited monitoring; efficacy is assessed during periodic clinical visits, often missing nuanced changes	[170]
Safety profile	Herbal treatments, when monitored digitally, minimise side effects by tailoring dosages and combinations for individual needs	Conventional synthetic drugs often have significant side effects, including addiction or withdrawal risks	[171]
Adherence	Mobile apps and telehealth platforms provide reminders, feedback, and symptom tracking, improving adherence	Adherence is lower due to a lack of continuous monitoring or patient engagement tools	[172]
Accessibility	Telehealth platforms enable remote consultations and personalised care for underserved or rural populations	Access to care is limited in remote areas, requiring frequent in-person visits for adjustments	[173]
Cost-effectiveness	Wearables and digital platforms reduce healthcare costs by decreasing the need for frequent in-person visits	Conventional care often involves repeated clinical visits and expensive pharmaceutical treatments	[174]
Holistic approach	Combines mood-enhancing and anxiolytic properties of herbs with VR-based therapies and stress-tracking devices for a multidimensional approach	It mainly focuses on pharmacological effects without addressing lifestyle, psychological, or environmental factors	[175]

Table 4 Continued

Category	Digital health + herbal treatment	Conventional method	Reference
Rapid feedback loop	Digital tools facilitate quick identification of ineffective treatments, allowing for rapid adjustment or switching	Treatment adjustments are delayed until follow-up appointments, prolonging the trial-and-error period	[176]
Empowerment	Patients are actively involved in their care, using apps to track progress and make informed treatment decisions	Patients rely solely on providers' guidance without tools to monitor their health independently	[177]
Combination therapy	Digital tools enable simultaneous tracking of herbal and non-herbal interventions for synergistic effects (e.g., acupuncture + herbs)	Conventional methods often lack integration with complementary therapies or focus solely on pharmaceuticals	[178]

11 Future perspectives

Due to the disease's heterogeneity, the diagnostic and treatment options for MDD are limited, and the pathological and pharmacological mechanisms by which it manifests are not yet understood. The majority of MDD patients do not have a good response to the antidepressants that are now available, even though SSRIs and SNRIs are the first-line therapy for MDD in the clinic. Research on real-world sequential therapy shows that about 30% of MDD patients still do not achieve remission despite multiple treatment efforts. This indicates that further study into the pharmacological processes of existing antidepressants is still required and that present ideas and hypotheses do not adequately explain the pathophysiology of MDD. From the vantage point of several popular hypotheses, including the neuroplasticity, HPA axis, cytokine, neurotransmitter and receptor, and systemic effect hypotheses, we primarily addressed the possible origins and pathophysiology of MDD. We may be able to alleviate the suffering and misery caused by severe depression if we had a better grasp of the pathophysiological underpinnings of MDD. This would allow us to create more effective therapeutic and preventative measures. New treatments can be better understood if we know more about the biological mechanisms that generate these changes and the symptoms they bring on.

New, safer, less intrusive, and easier-to-tolerate treatments will be made possible by technological advancements in the future. This can only be achieved with the help of significant, well-planned investigations. Research into functional magnetic resonance imaging (fMRI) indicators of the antidepressant effect of rTMS is ongoing in one such study [179]. Additional research is underway to determine whether EEG variables may be used to indicate rTMS efficacy. We need a better grasp of the specific mechanisms of neuromodulation treatments to develop better methods of treating these conditions. By integrating clinical trials with mechanistic investigations like neuroimaging, we can better understand the brain circuit changes linked to successful therapy and identify possible response biomarkers. This study can enhance our present neuromodulation methods while revealing potential new therapy targets.

Some herbs have been suggested in traditional medicine to alleviate stress, lift one's spirits, and lessen the severity of sleep problems [180]. Limitations such as small sample size, use of a single dose of the medicine, and short treatment periods are common in clinical research undertaken on the antidepressant effects of medicinal plants. The sample size heavily influences the study's findings; a small sample size makes it highly improbable that a statistically significant difference would be achieved. While it would be more accurate to compare medicinal plants' antidepressant effects to those of conventional antidepressants, much research has just compared them with the placebo. Most clinical investigations examining the antidepressant effects of medicinal plants have examined disease symptoms both before and several weeks after the intervention; nevertheless, the benefits of some herbs are noticeable right away, while others take longer. As an example, a scientific investigation found that curcumin did not start showing substantial antidepressant benefits until four weeks following treatment. Still, those effects did begin to materialise between weeks 4 and 8 [181]. So, it's best to check in on the symptoms once a week during treatment.

Factors such as genetic variation, region, harvest timing, soil quality, plant portion utilised, and processing techniques might affect the quantity and composition of plant chemicals. Therefore, producing herbal medications with a precise and consistent ingredient is challenging. Although preclinical research utilising plant active components appears to be effective, there is no way to ensure that complete extracts will be effective in clinical trials [182].

Capsules, pills, and drops containing medicinal compounds from *Hypericum perforatum, Matricaria recutita,* and *Valeriana officinalis* are available for purchase. These products are recommended for various uses, including relaxation, anxiety relief, depression treatment, and better sleep. It is necessary to do extensive safety tests on the herbs and get legal licenses from the food and medication administration or equivalent organisations before putting them on the market in medication form.

Future treatment of MDD will call for the harmonious integration of traditional herbal medicine with the latest digital health technologies. Looking ahead, a more

patient-centric approach with the help of digital tools assures personalised, effective, and scalable solutions for managing depression. Digital clinical trials would authenticate the phytochemicals in combining therapies with digital remedies. Research studies could also effectively employ telehealth platforms to reach diverse populations, especially hard-to-reach or underserved areas. Using AI and big data analysis of patient information from wearables, mobile apps, and digital biomarkers will likely unveil patterns leading to more predictable treatment responses. This could open new avenues of research into which herbs are best suited for particular subtypes of depression. Telemedicine would, therefore provide access to herbal treatment and digital therapy, mainly for the low-income population who may not readily have access to these conventional antidepressants. Plans for personal treatment outside the hospital can be provided for every patient and followed up regularly through remote digital services platforms. There are online educational resources and support communities. Such knowledge empowers a patient to actively participate in the treatment journey. This includes the treatment of herbs, their concentrations, and how to follow the progress through digital tools. Thus, the combination of digital innovation with traditional phytotherapy might be more promising for stronger, easier, and more individualised treatments in relation to depression. A focus on combining natural remedies and technology would form a complete program to deal with all the complexities of MDD while reducing side effects and engaging patients more purposefully.

12 Conclusion

Finally, while typical antidepressants may alleviate some depression symptoms in some people, they always come with the potential for side effects or recurrence. Additional research is required to determine whether the proposed therapy mechanisms are compatible with disease mechanisms, even though specific newly developed treatment strategies can alleviate depression symptoms in a specific program. Another promising frontier in treating MDD is combining digital technologies with traditional herbal therapies. While conventional antidepressants have continued to prove effective for most patients, they usually come with a great deal of unwanted side effects and variability in patient responses. By contrast, phytochemicals of medicinal herbs are relatively more natural and safer alternatives with fewer side effects. Mobile apps, wearable devices, AI-driven diagnostics, and platforms for telemedicine are changing the diagnosis, tracking, and treatment face of depression. Using these technologies together allows healthcare providers to offer patients a personalised, data-driven approach to herbal treatment tailored to their specific needs. Future research would focus more on large-scale digital clinical trials and the development of genomic data-integrated real-time patient feedback via AI-powered platforms. It may further facilitate deeper insights into the mechanisms of herbal drugs and the rationale for precision medicine so that both the traditional and emerging digital therapeutic strategies can be optimised.

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Competing interests

The authors declare no conflict of interest.

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中草药治疗重度抑郁症的数字及传统治疗策略最新进展

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【摘要】将数字健康技术如手机应用软件和数字生物标志物等与传统中草药和植物中含有的化学物质相结合，可以增强标准抗抑郁药物的疗效。目前，植物化学物与数字健康工具治疗抑郁症的作用机制已达成共识，而传统中草药和植物化学物也可能会增强标准抗抑郁药物的疗效。因此，本文不仅对植物化学物与中草药结合治疗抑郁症的已知机制做进一步补充说明，还结合数字创新技术和本草疗法，探讨了重度抑郁症的最新诊疗和预防手段。

【关键词】氟西汀；重度抑郁障碍；中草药；神经系统疾病；抑郁症；数字健康