Natural medicine-empowered treatment of depression via restoring neurogenesis (Review)

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Abstract. Major depressive disorder (MDD) remains a leading cause of disability, with a substantial proportion of patients failing to achieve adequate remission following conventional monoaminergic antidepressant treatment. The present narrative review examines evidence primarily published between 2015 and 2025 concerning natural medicines, including phytochemicals, traditional formulations, marine-derived products and dietary polyphenols, that may modulate neurogenesis relevant to depression. Adult hippocampal neurogenesis is regarded as one mechanistic framework rather than the sole explanation for depressive pathology. Priority was given to clinical and human-derived evidence, while preclinical studies are employed to elucidate underlying mechanisms. Natural products appear to converge on pathways involving brain-derived neurotrophic factor/tropomyosin receptor kinase B, Wnt/β-catenin, NF-κB/NLR family pyrin domain containing 3-mediated immune regulation, autophagy, mitochondrial bioenergetics and the gut microbiota. Nevertheless, current clinical evidence remains insufficient to support the use of natural medicines as substitutes for established antidepressant therapies. Their most plausible near-term application lies in standardized adjunctive or investigational interventions, pending larger biomarker-stratified trials, rigorous safety assessment and optimized formulation strategies.

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1. Introduction

Major depressive disorder (MDD) continues to impose a substantial global health burden. According to the World Health Organization, depression affects ~332 million people worldwide, corresponding to 4.0% of the global population and 5.7% of adults. Prevalence is higher among women (6.9%) than men (4.6%), and an estimated 727,000 people died by suicide in 2021 (1). Despite the widespread availability of pharmacological interventions, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), a considerable proportion of patients exhibit suboptimal treatment responses, with remission rates frequently remaining <50% even after multiple therapeutic attempts (2). This persistent therapeutic gap highlights the inherent limitations of conventional monoaminergic antidepressants, which primarily target neurotransmitter systems but often fail to address the complex and multifactorial pathophysiology present across individuals. The characteristic delayed onset of these treatments, often extending over weeks to months, combined with common adverse effects, further highlights the urgent need for innovative strategies capable of providing more rapid, sustained and comprehensive symptom relief (3,4).

Over the past decade, restoration of impaired hippocampal neurogenesis has emerged as a key mechanism in depression research. Adult hippocampal neurogenesis (AHN), the generation of new neurons from neural stem cells (NSCs) in the subgranular zone (SGZ) of the dentate gyrus (DG), contributes to hippocampus-dependent learning, memory, pattern separation and affective regulation (5-7). Preclinical studies, alongside selected human post-mortem analyses, link chronic stress and depression with reductions in AHN (8-10). Nevertheless, AHN should be considered within the context

of a broader neurobiological network that encompasses synaptic plasticity, glial-immune signaling, stress circuitry and network-level adaptations. Accordingly, the present review employs neurogenesis as a focused organizing framework without assuming it represents the sole causal mechanism or therapeutic target in MDD.

The present narrative review summarizes research published between 2015 and 2025 on natural medicines for depression, with particular emphasis on neurogenesis-related mechanisms and clinical translation. Priority was given to human clinical trials, post-mortem human studies and human-derived *in vitro* models, while animal and cellular studies were primarily used to elucidate underlying mechanisms. Natural products are discussed according to compound class, formulation strategy, evidence level and pathway involvement, including brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B (TrkB), Wnt/β-catenin, NF-κB/NLR family pyrin domain containing 3 (NLRP3), epigenetic regulation, mitochondrial bioenergetics, autophagy and gut-brain communication. Comparisons with SSRIs, SNRIs, ketamine, electroconvulsive therapy (ECT), psychotherapy and lifestyle interventions are framed to identify complementary roles and translational gaps rather than to imply overall superiority or clinical replacement.

Review methodology and evidence interpretation. The present article is a narrative review rather than a systematic review or meta-analysis. To enhance transparency, relevant literature was identified through targeted searches of PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/) and Google Scholar (https://scholar.google.com/) for English-language publications primarily from January 2015 to April 2025. Search terms combined 'depression' or 'major depressive disorder' with 'neurogenesis', 'adult hippocampal neurogenesis', 'BDNF', 'Wnt/β-catenin', 'neuroinflammation', 'autophagy', 'gut microbiota', 'natural products', 'natural medicines', 'phytochemicals', 'traditional Chinese medicine', 'polyphenols', 'nanomedicine', and related compound names.

Studies were included if they addressed depression or depression-relevant models, natural products or natural product-derived interventions, neurogenesis-related mechanisms, clinical translation, safety or formulation considerations. Priority was given to peer-reviewed clinical trials, human post-mortem studies, human-derived *in vitro* models and recent mechanistic animal studies. Publications that were not directly relevant to depression or neurogenesis, duplicate reports, non-peer-reviewed material or studies lacking interpretable mechanistic or therapeutic information were excluded.

Evidence was interpreted hierarchically: Randomized clinical trials and meta-analyses were weighted most strongly; human observational studies, post-mortem analyses and human-derived cellular studies were considered supportive; animal and cellular studies were primarily used to clarify underlying mechanisms. As a narrative review, a formal risk-of-bias assessment was not applied. Instead, study design, sample size, control measures, reproducibility, outcome metrics and the preclinical vs. clinical nature of the evidence were qualitatively considered. Preclinical efficacy was not regarded as equivalent to clinical efficacy.

2. Neurogenesis hypothesis of depression and its impairment

The relationship between AHN and mood regulation has evolved from a theoretical concept to a well-characterized biological process implicated in the pathophysiology of MDD. AHN refers to the ongoing generation of new neurons from NSCs in the SGZ of the DG within the hippocampus, a region essential for memory, learning and emotional processing (5-7). Newly generated neurons undergo a complex maturation process, integrating into pre-existing neural circuits and contributing to hippocampal plasticity and functionality, including pattern separation, spatial memory and regulation of affective states (11). Environmental factors such as exercise and enrichment have been shown to enhance AHN, whereas chronic stress, a primary risk factor for depression, consistently suppresses it (5,12).

Evidence for impaired neurogenesis in depression. Preclinical studies demonstrate that multiple animal models of depression, particularly chronic stress paradigms, exhibit reductions in AHN. This impairment encompasses decreased proliferation of NSCs, diminished survival of newly generated neurons, and altered differentiation, collectively reducing the pool of functional adult-born neurons. For instance, chronic corticosterone administration in mice induces depressive-like behaviors, decreases hippocampal BDNF expression and disrupts AHN. Mechanistically, these effects have been linked to hyperactive neuronal autophagy, increased autophagy protein 5 (ATG5) expression, and lysosomal degradation of BDNF. Silencing Atg5 reverses these alterations, suggesting that neuronal autophagy may mediate the connection between chronic stress, BDNF depletion and AHN inhibition (9,13). Additionally, chronic unpredictable stress and corticosterone exposure suppress adult neurogenesis and reduce hippocampal astrocyte populations in murine models, further supporting the association between stress exposure and neurogenic deficits (14).

Beyond its direct effects on neurogenesis, neuroinflammation, a dysregulated immune response within the brain, has gained increasing recognition as a critical factor in MDD and a potent disruptor of hippocampal neurogenesis (15). Inflammatory cells, including microglia, astrocytes and oligodendrocytes, serve central roles in shaping the neurogenic microenvironment. Dysregulated microglial activity has been implicated in the disruption of neurogenesis and constitutes a key component of depression pathophysiology, involving mechanisms such as Toll-like receptor (TLR) signaling, microglial polarization and the release of inflammatory cytokines (15-18). Astrocytes also exhibit multifaceted roles; for example, signaling from astrocyte-derived chitinase-3-like protein 1 has been shown to impair neurogenesis and cognitive function by attenuating β-catenin signaling in hippocampal demyelination models (19). Collectively, these findings indicate that impairments in AHN within the context of depression are not merely secondary consequences but actively contribute to disease manifestation, shaped by the intricate interplay among stress hormones, neurotrophic factors and inflammatory pathways.

Human adult hippocampal neurogenesis: Recent developments and challenges. The existence and functional relevance

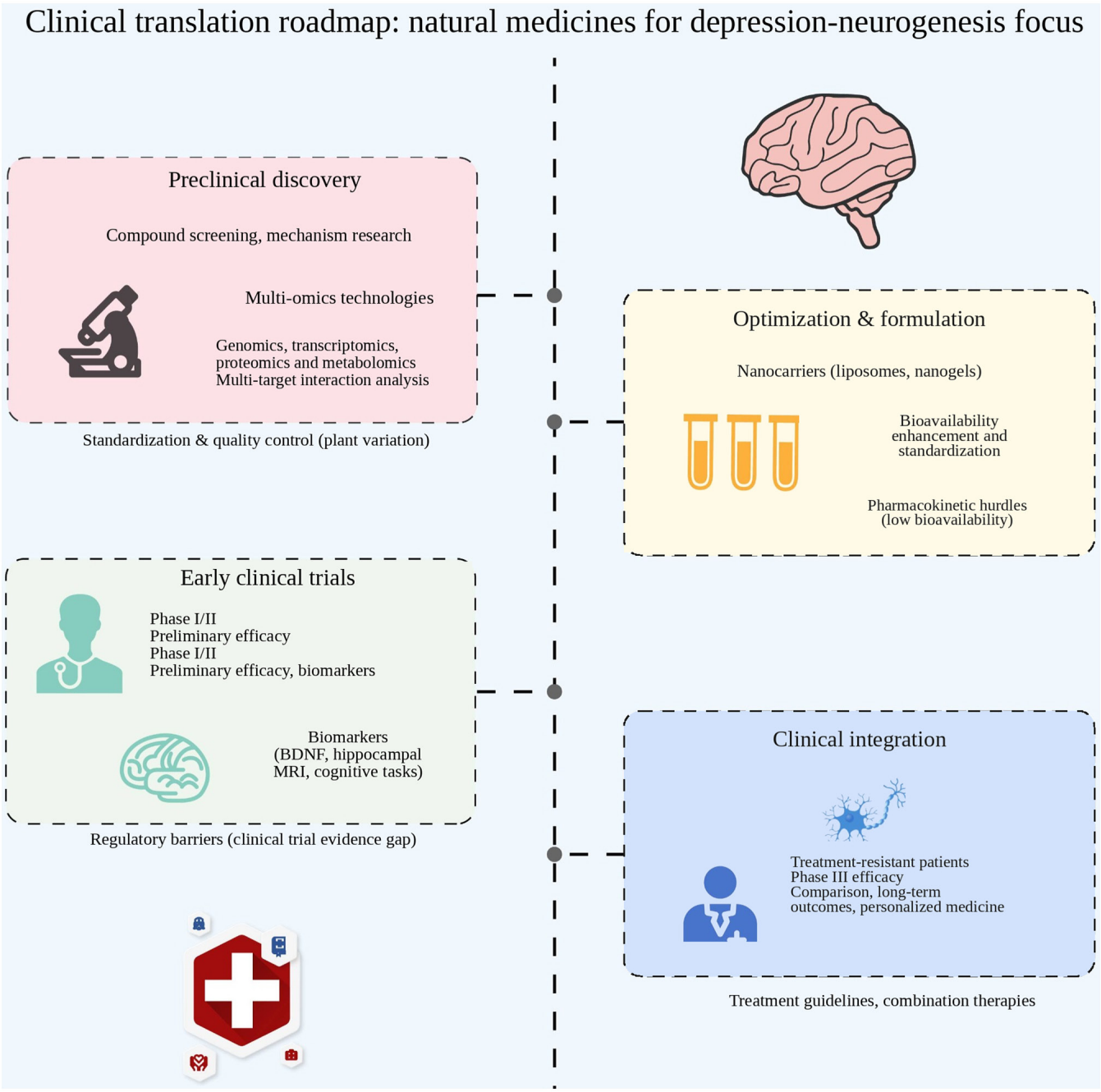

Figure 1. Integrated mechanism network linking natural medicines to neurogenesis-related antidepressant effects. Natural products and formulations may converge on BDNF/TrkB, Wnt/β-catenin, NF-κB/NLRP3-mediated immune regulation, autophagy, mitochondrial bioenergetics and gut microbiota signaling; these pathways support synaptic plasticity and hippocampal neurogenesis but require clinical validation. BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B, NLRP3, NLR family pyrin domain containing 3.

of AHN in the human brain have been subjects of extensive scientific investigation. Early post-mortem studies provided evidence supporting ongoing neurogenesis; however, subsequent reports yielded conflicting results, with some suggesting that neurogenesis ceases by early childhood (7,20). Recent technological advances, particularly in single-cell transcriptomics and refined immunohistochemical techniques, now allow more precise characterization of AHN in humans. Current research is exploring complex cell fate decisions within the developing human neocortex, revealing substantial direct neurogenesis that bypasses intermediate progenitors, a process critical for cortical expansion in gyrencephalic species (21-24).

Despite these advancements, mapping human AHN via single-cell transcriptomics continues to face methodological, conceptual and biological challenges that require consistent resolution across studies (25). The relative scarcity of radial glial cells in humans compared with other species further complicates understanding of macroglial dynamics and the evolutionary aspects of adult neurogenesis (26). Nevertheless, a growing consensus recognizes the presence of AHN in humans, albeit with potentially distinct dynamics and regulatory mechanisms relative to rodent models. For example, glucocorticoids have been shown to modulate human cortical neurogenesis by enhancing a specific subtype of basal

progenitors, providing a cellular and molecular framework for understanding how glucocorticoids influence postnatal neurogenesis (27). Such research is essential for translating findings from animal models into therapeutic strategies for humans.

BDNF as a central regulator. BDNF is a key neurotrophin involved in neurogenesis and depression pathophysiology, regulating synaptic growth, plasticity and neurotransmission, and notably influencing learning, memory and depression-associated behaviors (28). The neurotrophic hypothesis of depression posits that reduced BDNF levels contribute to MDD pathophysiology, with effective antidepressant interventions enhancing BDNF expression and signaling. Meta-analyses support this view, showing markedly lower serum exosomal BDNF levels in patients with MDD, which increase following pharmacological treatment, indicating the role of BDNF in both disease pathophysiology and treatment response (29,30).

BDNF exerts its biological effects primarily through TrkB, activating intracellular cascades such as PI3K/Akt, MAPK/ERK and PLCγ, which coordinate neuronal survival, differentiation and synaptic plasticity (28). Disruption of BDNF/TrkB signaling is associated with reduced neurogenesis and depressive phenotypes, whereas interventions that enhance BDNF expression or downstream signaling remain promising yet require careful translational evaluation. The BDNF-interactive model further suggests that environmental enrichment, physical activity, cognitive stimulation and mindfulness may modulate BDNF and related growth factors to sustain neurogenesis in humans (31).

3. Natural medicines: A new frontier for depression treatment

The persistent global burden of MDD and the limitations of conventional pharmacological treatments have stimulated extensive investigation into alternative and complementary therapeutic approaches. Among these, natural medicines, including plant-derived compounds, traditional formulations, marine products and dietary constituents, have emerged as a particularly promising area of research. Their long-standing use across diverse cultures, together with a growing body of scientific evidence, positions them as valuable candidates for addressing the multifactorial pathophysiology of depression, particularly through mechanisms related to the restoration of neurogenesis.

Promise and complexity of natural products in drug discovery. Natural products have constituted a vital source of therapeutic agents for centuries and have inspired the development of numerous modern pharmaceuticals (32). The notable chemical diversity found in nature provides a unique reservoir for the identification of novel bioactive compounds with diverse pharmacological activities. Unlike synthetic drugs, which are frequently designed to target a single molecular pathway, natural products often exert polypharmacological effects through simultaneous engagement of multiple biological targets. This multitarget mode of action is increasingly recognized as advantageous for complex, multifactorial disorders such as depression, in which single-target interventions may be insufficient to address the intricate network of pathological processes involved (33-35). The concept of a 'neg-entropy mechanism' as a therapeutic target for natural medicines, proposed by Gao *et al* (33) in 2024, reflects this integrative perspective by suggesting that the conventional drug-discovery paradigm centered on individual molecular targets may be overly restrictive for chronic diseases. Instead, this framework advocates the development of therapeutic agents capable of restoring systemic homeostasis through coordinated interactions with multiple targets. Such a perspective aligns closely with the complex pathophysiology of depression, which involves neuroinflammation, oxidative stress, dysregulation of neurotrophic factors and impaired neurogenesis.

Recent advances in medicinal chemistry and mechanistic biology have further strengthened interest in the therapeutic potential of natural medicines. Special issues on Natural Medicine, highlighted by Jiang (36), showcase a broad spectrum of research spanning individual botanical compounds, complex plant-based formulations, and reviews addressing bile acids and synthetic bear bile, thereby emphasizing innovative research directions. Reviews by Luo *et al* (37) and Balkrishna *et al* (38) highlight substantial progress in elucidating the safety, efficacy and bioactivity of herbal medicines, helping to bridge traditional knowledge and contemporary scientific investigation. Certain compound classes, including chromones and chromanones, have demonstrated diverse biological activities, notably antioxidant and anti-inflammatory effects.

The antimicrobial and antiviral properties of certain natural compounds position them as promising candidates for drug development, although their safety profiles require evaluation on a compound-specific basis (39). Polyphenols, in particular, are recognized for their antioxidant and anti-inflammatory activities, offering potential therapeutic approaches for neurodegenerative disorders by mitigating oxidative stress and suppressing inflammatory cytokines (40). Nonetheless, the inherent complexity of natural products presents considerable challenges. Variability in the chemical composition of herbal extracts is influenced by factors such as geographical origin, harvesting practices, processing methods and storage conditions, resulting in difficulties in standardization and reproducibility of research outcomes (41,42). Identification of bioactive constituents within complex mixtures, scaling up production and maintaining consistent quality control remain notable obstacles (32,43). Despite these challenges, the integration of high-throughput omics technologies, including genomics, transcriptomics, proteomics and metabolomics, is driving a transformative phase in natural drug discovery. These approaches provide unparalleled insights into the chemical diversity, biosynthesis and mechanisms of action of bioactive compounds derived from medicinal plants (44,45). Network pharmacology methodologies have emerged as particularly valuable, enabling the systematic elucidation and visualization of intricate interaction networks of Traditional Chinese Medicines (TCMs) in the context of multifactorial diseases, thereby facilitating the identification of lead compounds from complex multi-component to target protein/disease networks (34,35,46).

Nanotechnology for enhanced delivery and efficacy. A major limitation of numerous natural compounds is their poor

solubility in aqueous environments, low bioavailability and susceptibility to degradation, which constrain therapeutic efficacy. Nanotechnology offers innovative solutions by enabling the development of advanced drug delivery systems that enhance the stability, solubility, and targeted delivery of natural medicines (47-53). Nanocarrier drug delivery systems (NDDS), including liposomes, polymeric nanoparticles, micelles and exosome-like vesicles, can encapsulate natural compounds, protecting them from degradation, improving pharmacokinetic profiles and facilitating transport across biological barriers, including the blood-brain barrier (BBB) (51,53).

Recent studies and reviews highlight the substantial potential of nanotechnology to enhance the efficacy of natural medicines in depression (30,53,54). Engineered rabies virus glycoprotein (RVG)-BDNF exosomes, designed to overexpress BDNF, have demonstrated the ability to cross the BBB and selectively target neurons in the hippocampus and prefrontal cortex in mouse models of depression. This targeted delivery elevates BDNF levels, ameliorates depressive-like behaviors, reduces neuroinflammation and promotes neurogenesis and synaptic plasticity (30). Similarly, BDNF-quercetin alginate nanogels exhibit uniform particle size, biocompatibility and potent antioxidant and anti-inflammatory properties, achieving sustained BDNF release, rapid brain distribution and markedly improved bioavailability compared with orally administered quercetin. Across these preclinical studies, the engineered exosomes and nanogels produced antidepressant-like effects in animal models, with the nanogels additionally modulating glutamatergic, PI3K-Akt and BDNF-TrkB signaling pathways (30,54).

In addition to enabling targeted delivery, nanotechnology can be employed to develop novel therapeutic agents derived from natural sources. For instance, melanin-like polydopamine nanoparticles (PDA NPs) have been synthesized owing to their notable antioxidant properties and ability to traverse the BBB. *In vivo* investigations have demonstrated that PDA NPs can reverse depression-like behaviors in mice subjected to lipopolysaccharide-induced inflammation, resulting in reductions in both peripheral and central inflammation, attenuation of microglial activation and restoration of synaptic integrity (55). Additionally, self-assembled products derived from Chinese Herbal Medicines (CHMs) are currently under investigation as potential therapeutic agents.

Effective nanomedicines have become pivotal components in the formulation of CHMs, with pharmacologically active nanoparticles serving essential roles. These include various entities such as nanoaggregates, exosome-like vesicles and self-assembled structures of natural compounds, which not only address existing challenges but also facilitate the modernization of CHM (49,50). Moreover, advanced mass spectrometry techniques are being refined for *in vivo* evaluation of natural medicines, enabling the identification of bioactive constituents and pharmacokinetic markers within these complex nano-formulations (56). The integration of nanotechnology with natural medicine research represents a robust strategy for overcoming bioavailability limitations, enhancing targeted delivery and ultimately improving therapeutic outcomes in conditions such as depression.

4. Plant-derived compounds and traditional formulas targeting neurogenesis

Over the past decade, there has been a substantial increase in research investigating plant-derived compounds and traditional herbal formulations, particularly with respect to their antidepressant potential and their capacity to restore impaired neurogenesis. These natural products often exhibit a complex array of pharmacological activities that target multiple aspects of depression pathophysiology, including neuroinflammation, oxidative stress and dysregulation of neurotrophic factors, all of which converge on neurogenic processes.

Promising plant-derived compounds and their neurogenic mechanisms. A diverse range of plant-derived compounds has demonstrated considerable potential for modulating neurogenesis and mitigating depressive symptoms. These compounds generally exert their effects through the coordinated action of anti-inflammatory, antioxidant and neurotrophic mechanisms, highlighting their polypharmacological nature. As summarized in Table I (54,57-67), Ginsenoside Re (Gs-Re), derived from *Panax ginseng*, consistently exhibits neuroprotective effects through robust activation of the BDNF/TrkB/ERK/cAMP response element-binding protein (CREB) signaling cascade, which is critical for neuronal survival and plasticity. Through this mechanism, Gs-Re alleviates neurogenic impairments induced by oxidative stress and inflammation (57). Such multifaceted pharmacological activities support further investigation of Gs-Re as a candidate compound for the modulation of neurogenesis. Similarly, Echinacoside (ECH), isolated from *Echinacea* and *Cistanche*, not only enhances CREB-BDNF signaling but also exerts pronounced immunomodulatory effects by inhibiting M1 microglial polarization and suppressing the secretion of inflammatory mediators (58). Moreover, its unique capacity to upregulate nuclear factor erythroid 2-related factor 2 (Nrf2) through acetylation further highlights its broad neuroprotective and neurogenic potential, particularly in inflammatory conditions such as post-stroke depression (59).

Quercetin, a well-characterized flavonoid, exemplifies the challenges associated with the bioavailability of natural compounds while simultaneously demonstrating therapeutic promise in preclinical investigations and delivery-system-based studies (40,54). When delivered using innovative BDNF-quercetin alginate nanogels, its potent antioxidant and anti-inflammatory properties are leveraged to regulate glutamatergic, PI3K-Akt and BDNF-TrkB signaling pathways, leading to markedly enhanced antidepressant efficacy and restoration of neurogenesis (54). Curcumin, the principal curcuminoid present in turmeric, further illustrates the multitarget pharmacological profile of these natural compounds. Its ability to rescue impaired neurogenesis, including in models of Alzheimer's disease, is closely linked to the modulation of the PI3K/Akt, GSK3β/Wnt/β-catenin and CREB/BDNF signaling pathways, with Wnt/β-catenin and BDNF signaling serving as key mediators of these effects (60).

In addition to directly supporting neurotrophic processes, certain compounds also counteract neurogenic deficits driven by neuroinflammation. Phloretin (PHL), a dihydrochalcone derived from apples, alleviates depression-like behaviors by

Table I. Selected natural products and formulations with neurogenesis-related mechanisms and evidence level.

Compound/formulation	Source	Key neurogenic mechanisms	Evidence base	(Refs.)
Ginsenoside Re	*Panax ginseng*	BDNF/TrkB/ERK/CREB activation; antioxidant and anti-inflammatory effects; anti-apoptotic signaling.	Preclinical *in vivo*/*in vitro*	(57)
Echinacoside	*Echinacea* spp.; *Cistanche deserticola*	CREB-BDNF enhancement; reduced M1 microglial polarization; Nrf2-related regulation.	Preclinical *in vivo*/*in vitro*	(58,59)
Quercetin	Widely distributed flavonoid	BDNF-TrkB, PI3K-Akt, and glutamatergic modulation; antioxidant and anti-inflammatory effects.	Preclinical, including delivery-system models	(54)
Curcumin	*Curcuma longa*	Wnt/β-catenin, PI3K/Akt, and CREB/BDNF pathway regulation.	Preclinical mechanistic evidence	(60)
Phloretin	Apples and other fruits	NF-κB-C3 inhibition; reduced microglial activation and synaptic engulfment.	Preclinical stress/inflammation models	(61)
Naringenin	Citrus fruits	Anti-inflammatory and neurogenic effects through multiple pathways.	Preclinical evidence	(62,63)
Salidroside	*Rhodiola crenulata*	HSC70 activation and enhanced BDNF/TrkB signaling.	Preclinical evidence	(64)
Catalpol	*Rehmannia glutinosa*	Neurogenesis and angiogenesis via SDF-1α/CXCR4 signaling.	Preclinical evidence	(65)
Gallic acid	Various plants	GSK-3β-Nrf2 pathway modulation; neurogenesis support.	Preclinical evidence	(66)
Niuhuang Qingxin Wan	Traditional formulation	TrkB/ERK/CREB modulation and hippocampal neurogenesis in stress models.	Preclinical formulation evidence; clinical relevance requires trials	(67)

BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B, NLRP3, NLR family pyrin domain containing 3; CREB, cAMP response element-binding protein; Nrf2, nuclear factor erythroid 2-related factor 2; HSC70, heat shock cognate protein 70; SDF-1α, stromal cell-derived factor 1; CXCR4, C-X-C chemokine receptor type 4.

inhibiting the NF-κB-C3 axis, thereby suppressing microglial activation and reducing microglia-mediated synaptic engulfment, representing a novel mechanism of antidepressant action (61). Naringenin, a flavonoid obtained from citrus fruits, similarly contributes to this therapeutic landscape. Furthermore, multiple compounds enhance neurogenesis while concurrently mitigating inflammation through diverse signaling pathways, reflecting a dual-target strategy in the treatment of depression (62,63). Salidroside, isolated from *Rhodiola crenulata*, exerts neuroprotective effects by activating heat shock cognate protein 70, which in turn enhances BDNF/TrkB signaling and promotes neurogenesis. Although this mechanism was initially investigated in stroke models, it is particularly relevant to mood disorders (64). Catalpol, an iridoid glycoside, facilitates both neurogenesis and angiogenesis via the stromal cell-derived factor 1/C-X-C chemokine receptor type 4 pathway, which is essential for maintaining a healthy neurogenic environment, suggesting its potential utility in conditions characterized by compromised neurovascular integrity (65). Additionally, gallic acid (GA), a phenolic acid, stimulates neurogenesis through the GSK-3β-Nrf2 pathway by directly inhibiting GSK-3β, highlighting mechanistic overlap in the neurobiological deficits observed in both Alzheimer's disease and depression (66). Collectively, these compounds exemplify the diverse yet convergent strategies employed by plant-derived natural products to promote neurogenesis.

Formulations of TCM. Formulations in TCM, characterized by their multi-component and multi-target properties, constitute a substantial reservoir of potential antidepressant therapies, frequently targeting pathways associated with neurogenesis either implicitly or explicitly. The holistic philosophy underlying TCM aligns closely with the complex pathophysiology of depression, and contemporary research increasingly employs advanced methodologies, such as network pharmacology, to elucidate their mechanisms of action.

Niuhuang Qingxin Wan (NHQXW), a widely studied TCM formulation, has demonstrated antidepressant-like effects and the capacity to enhance hippocampal neurogenesis in chronic stress models. Du *et al* (67) reported that NHQXW markedly attenuated depressive-like behaviors and promoted hippocampal neurogenesis by modulating the expression of BDNF, TrkB, phosphorylated (p)-ERK, p-MEK1/2 and p-CREB. These findings indicate that NHQXW exerts its effects via the

BDNF/TrkB/ERK/CREB signaling pathway, which is critical for neuronal survival and plasticity. Notably, the antidepressant efficacy of NHQXW was comparable to that of fluoxetine, with the added advantage of effectively preventing rebound symptoms following withdrawal, suggesting a favorable profile in both efficacy and tolerability. Liquiritin, a bioactive constituent of NHQXW, has been identified as a key component driving neurogenesis. Collectively, these preclinical results support the potential of NHQXW as a candidate TCM formulation for further investigation in chronic stress and depression, particularly through mechanisms involving hippocampal neurogenesis and neurotrophic factor signaling.

The modernization of TCM is increasingly supported by advanced scientific approaches. Yao *et al* (68) reviewed the modulation of the vitamin D receptor by TCM formulations and bioactive compounds, highlighting its pivotal role in brain-relevant physiological processes. Network pharmacology has emerged as a transformative tool for the study of TCMs, enabling the visualization and analysis of complex interactions between multiple compounds and their diverse biological targets. For example, Li *et al* (34) emphasized the utility of network pharmacology as an innovative approach for TCM-based drug discovery targeting multifactorial diseases, elucidating molecular-protein interactions and aiding in the identification of lead compounds (35). The TCMs-Compounds Functional Annotation platform, an evidence-based data mining tool, exemplifies this progress by facilitating the rapid discovery of novel bioactive compounds, as demonstrated in studies focused on myocardial protection (46). Such advancements are critical for the modernization and international recognition of TCM, providing a robust scientific framework to support their efficacy in conditions such as depression, particularly by clarifying the mechanisms through which they promote neurogenesis (34,35,46).

5. Other natural products and modalities impacting neurogenesis

In addition to individual plant-derived compounds and traditional herbal formulations, several natural or nature-inspired interventions may modulate neurogenesis and depression-related biological processes. These include dietary nutrients, marine-derived products, selected psychoactive compounds, exercise-associated mediators, and extracellular vesicle-based approaches.

Dietary polyphenols and carotenoids. Dietary interventions, particularly those rich in polyphenols and carotenoids, are increasingly recognized for their potential to support brain health and regulate neurogenesis. Melgar-Locatelli *et al* (69) demonstrated that a high-phenolic cocoa diet markedly improved object recognition memory and enhanced AHN, accompanied by increased BDNF expression and proliferation of young adult neurons in murine models. These findings highlight the important role of cocoa flavanols in promoting brain health, likely through their antioxidant and anti-inflammatory properties as well as their direct modulation of neurotrophic factors, thereby offering a non-pharmacological approach to improving mental well-being.

Astaxanthin, a potent carotenoid derived from *Haematococcus pluvialis*, has attracted considerable attention because of its ability to cross the BBB and exert neuroprotective effects. Medoro *et al* (70) reviewed the emerging role of astaxanthin as an antioxidant and anti-inflammatory agent in the context of brain aging and adult neurogenesis. The authors highlighted that astaxanthin positively regulates adult neurogenesis through activation of FOXO3-related signaling pathways, promotion of cellular proliferation, and modulation of neuroinflammation via suppression of NFκB and reduction of pro-inflammatory cytokine production. By helping to restore a favorable neurogenic microenvironment, astaxanthin may contribute to the maintenance of neurogenic niches during aging, representing a potential strategy for mitigating age-related cognitive decline and potentially associated depressive disorders, which often share overlapping pathophysiological mechanisms. Furthermore, a neurogenesis-centered biological susceptibility framework has been proposed in relation to brain aging, whereby dietary and nutritional factors, including plasma lycopene and vitamin D levels, are associated with cognitive decline, dementia and depressive symptoms in older adults. These observations suggest that dietary factors may influence the risk of such outcomes in individuals susceptible to neurogenesis-related impairments (71).

Psychedelic substances. Psychedelic compounds, once largely restricted to the context of illicit use, have experienced a substantial resurgence in clinical research, particularly as potential treatments for treatment-resistant depression (TRD). Substances such as psilocybin, mescaline and lysergamides primarily influence perception, emotion and cognition through activation of serotonin 5-HT2A receptors (72).

Recent clinical studies have evaluated the therapeutic efficacy of psilocybin-assisted therapy in MDD. Agrawal *et al* (73) highlighted its potential as a scalable intervention capable of producing rapid antidepressant effects in patients with cancer with comorbid MDD. Sloshower *et al* (74) reported notable improvements in psychological flexibility, mindfulness and value-consistent living following treatment, with these benefits persisting over time and associating with reductions in depression severity, thereby supporting psychological flexibility as an important therapeutic mediator. In addition, Back *et al* (75) investigated psilocybin-assisted therapy among clinicians experiencing depressive symptoms associated with frontline COVID-19 care, further expanding the available evidence base.

Nevertheless, important uncertainties remain. Erritzoe *et al* (76) reported that patients who discontinued SSRIs or SNRIs before undergoing psilocybin therapy exhibited smaller treatment responses than patients without prior exposure to these medications, suggesting that previous serotonergic antidepressant use may influence therapeutic outcomes following psilocybin administration. Weiss *et al* (77) found that both psilocybin therapy and escitalopram were associated with favorable changes in personality measures; however, the study did not establish a distinct or unique effect of psilocybin on personality. Direct evidence demonstrating that psilocybin enhances neurogenesis in humans remains limited. Consequently, its relevance to the present review is more appropriately interpreted in terms of its broader effects on neuroplasticity, psychological flexibility and neural circuit remodeling.

Exerkines and exosomes. The beneficial effects of physical exercise on mental health are well-established, and recent studies have identified molecular mediators known as 'exerkines'. For example, Leiter *et al* (78) highlighted the platelet-derived exerkine CXCL4, also known as platelet factor 4 (PF4), as a critical mediator of exercise-induced rejuvenation in the brain. Physical activity activates platelets, which release PF4, thereby promoting the proliferation of hippocampal precursor cells and enhancing cognitive function in aged murine models. This pioneering work elucidates a novel mechanism through which exercise supports neurogenesis and restores cognitive function, positioning platelets as essential communicators between peripheral systems and the central nervous system.

In parallel, exosomes, small extracellular vesicles that mediate intercellular communication, are emerging as notable modulators of neurogenesis and potential therapeutic tools for depression. Mesenchymal stem cell (MSC)-derived exosomes have demonstrated the capacity to ameliorate neurodegenerative consequences associated with brain disorders. Fallahi *et al* (79) reported that MSC-derived exosomes enhanced neurogenesis and cognitive performance in mice with methamphetamine-induced neurotoxicity. Engineered RVG-BDNF exosomes, designed to deliver BDNF, efficiently cross the BBB and selectively target neurons in the hippocampus and prefrontal cortex, thereby reducing depressive-like behaviors, attenuating neuroinflammation, and promoting neurogenesis and synaptic plasticity in mouse models of depression (30). Similarly, oligodendrocyte-derived exosomes (ODEXs) containing sirtuin 2 (SIRT2) alleviate depressive-like behaviors and restore hippocampal neurogenesis and synaptic plasticity via the AKT/GSK-3β signaling pathway (80). Additionally, Hu *et al* (81) developed exosome-encapsulated, reactive oxygen species (ROS)-responsive nanogels for targeted treatment of perimenopausal depression, demonstrating effective cellular uptake, BBB penetration and rapid antidepressant effects by modulating pituitary adenylate cyclase-activating peptide/first procaspase activating compound-associated proteins involved in synaptic plasticity, while also exhibiting antioxidant and anti-inflammatory properties. Collectively, these studies highlight the therapeutic potential of both naturally occurring and engineered exosomes in promoting neurogenesis and ameliorating depressive pathology.

Nanoparticles and hydrogels. Beyond exosome-based nanocarriers, diverse nanoparticles and hydrogel systems are being developed to enhance the delivery and efficacy of natural compounds or to directly stimulate neurogenesis. Melanin-like PDA NPs have been synthesized due to their potent antioxidant properties and ability to cross the BBB. Zhu *et al* (55) demonstrated that PDA NPs reversed depression-like behaviors in mice subjected to lipopolysaccharide-induced inflammation, effectively reducing peripheral and central inflammation, diminishing microglial activation, and restoring synaptic integrity, thereby illustrating their potential for treating inflammatory depression.

Biomaterial-based strategies are also being explored for tissue repair and neuroregeneration. Zheng *et al* (82) developed an Nb_2C MXene-functionalized hydrogel for volumetric muscle loss, which supported myogenesis, angiogenesis, neural differentiation of MSCs and *in vivo* nerve regeneration. Hong *et al* (83) designed an annular conductive gelatin-methacrylic acid-polyaniline (Gel/Pani) hydrogel electrode responsive to wireless electrical stimulation, promoting neuronal development, functional neural network formation and neurological recovery in mice with ischemic stroke via enhanced neurogenesis. Decellularized extracellular matrix enriched with glial cell line-derived neurotrophic factor (GDNF) has been shown to promote neurogenesis and remyelination following spinal cord injury (84), and dual-layer microneedles releasing nitric oxide and oxygen improved diabetic wound healing through neurogenic, angiogenic and immunomodulatory mechanisms (85). Although these systems have not yet been applied to depression, they exemplify versatile delivery and regenerative platforms that could inform future interventions targeting neurogenesis.

6. Multi-target mechanisms underlying neurogenesis restoration

Natural medicines rarely exert their effects through a single molecular target. Their putative antidepressant properties are more plausibly attributed to coordinated modulation of neurotrophic signaling, inflammation, oxidative stress, mitochondrial function, autophagy and gut-brain communication (Fig. 1). The present section discusses these pathways while highlighting areas in which the current evidence remains predominantly preclinical.

Neurotrophic factor signaling pathway. Neurotrophic factors, particularly BDNF, are key regulators of neuronal survival, maturation and synaptic plasticity. Impaired neurotrophic support has been associated with depression-related phenotypes, and several natural compounds appear to modulate these pathways in preclinical models.

BDNF/TrkB signal. BDNF/TrkB signaling is among the most frequently reported targets of natural products. Gs-Re activates BDNF/TrkB/ERK/CREB signaling while mitigating oxidative stress and inflammation (57). ECH enhances the BDNF-CREB axis and modulates microglial polarization (58,59). Quercetin delivered via BDNF-quercetin alginate nanogels acts on BDNF-TrkB, PI3K-Akt and glutamatergic pathways (54). Curcumin, NHQXW and salidroside likewise modulate neurotrophic cascades relevant to neurogenesis (60,64,67). Collectively, these findings identify BDNF/TrkB as a recurring mechanistic node; however, the supporting evidence remains largely preclinical.

Wnt/β-catenin signaling. Wnt/β-catenin signaling regulates NSC proliferation, differentiation and neuronal maturation. Natural and dietary compounds, including curcumin and resveratrol, have been reported to modulate this pathway in models of neurological disease (86). In particular, curcumin restores impaired neurogenesis through activation of Wnt/β-catenin signaling, and inhibition of this pathway attenuates its neuroprotective and memory-related effects (60). Although vilazodone is a synthetic compound, evidence indicating that it preserves β-catenin signaling further supports the broader relevance of this pathway to emotional regulation and neurogenesis (87).

PI3K/Akt and ERK/CREB pathways. PI3K/Akt and ERK/CREB are major downstream effectors of neurotrophic signaling and regulate neural precursor survival, proliferation and synaptic plasticity. Several aforementioned interventions converge on these cascades: Gs-Re activates BDNF/TrkB/ERK/CREB signaling; quercetin nanogels modulate PI3K-Akt and BDNF-TrkB pathways; curcumin regulates PI3K/Akt together with Wnt/β-catenin and CREB/BDNF signaling; and NHQXW influences p-ERK and p-CREB levels (54,57,60,67). Exosome-based approaches and milk fat globule-EGF factor 8 protein further implicate AKT/GSK-3β and integrin β3/Akt signaling in AHN (80,88).

These convergent findings support a multi-target hypothesis in which natural products and nature-inspired delivery systems act through overlapping neurotrophic and survival pathways. Nevertheless, activation of these pathways in cellular or animal models should not be regarded as evidence of clinical antidepressant efficacy; confirmation through human studies incorporating biomarker-linked outcomes remains necessary.

Immunomodulation and neuroinflammation. Neuroinflammation, characterized by an atypical immune response within the brain, serves a central role in the pathophysiology of MDD and constitutes a major barrier to neurogenesis (8,10). Numerous natural medicines exert antidepressant effects through the modulation of neuroinflammatory processes.

Microglial polarization and cytokine modulation. Microglia, the resident immune cells of the brain, serve a dual role in neurogenesis: Dysregulated activity can impair neurogenesis, whereas appropriate regulation can promote it (15). Natural compounds frequently modulate microglial polarization. ECH has been shown to inhibit M1 polarization of N9 microglia and reduce the secretion of inflammatory factors, thereby maintaining microglial homeostasis and alleviating neuroinflammation (58). PHL suppresses microglial activation and phagocytic activity, resulting in reduced C3 deposition and microglia-mediated synaptic engulfment, which helps prevent chronic stress-induced depression-like behaviors (61). Melanin-like PDA NPs reduce both peripheral and central microglial activation and inflammation in models of inflammatory depression (55). Itaconate alleviates cognitive impairments induced by anesthesia or surgery by activating Nrf2-dependent anti-neuroinflammatory and neurogenic processes, thereby inhibiting the activation of microglia and astrocytes (89).

Natural medicines also directly modulate cytokine levels. ECH has been reported to reduce pro-inflammatory cytokine levels (58). Gs-Re decreases pro-inflammatory cytokines and counteracts neuroinflammation (57). Naringenin has been shown to alleviate depressive symptoms through the reduction of inflammation (62). Oxidative stress, which is often associated with inflammation, promotes neuroinflammation, neurodegeneration and neuronal death in depression; therefore, natural products with antioxidant properties may help attenuate these effects (10). Microglial activation and disruption of hippocampal neurogenesis mediated by IL-6 and IL-18 have been implicated in early neuropsychiatric lupus, highlighting the detrimental effects of these cytokines (16). Reviews have summarized the anti-inflammatory active constituents and mechanisms of action of natural medicines, with particular emphasis on signaling pathways such as NF-κB (38,40,90). TLRs, which are expressed in cells of the nervous system, also regulate neurogenesis, cognition and neuroinflammation, and may likewise be modulated by natural products.

NF-κB/NLRP3 and oxidative stress pathways. The NF-κB pathway is a central regulator of inflammation, and its activation typically induces the production of pro-inflammatory cytokines. PHL has been shown to inhibit the NF-κB-C3 axis, thereby exerting neuroprotective effects (61). Astaxanthin modulates neuroinflammation through suppression of NF-κB, resulting in reduced levels of pro-inflammatory cytokines and restoration of a neurogenesis-permissive microenvironment (70). Furthermore, exercise has been reported to enhance hippocampal neurogenesis in type 2 diabetes mellitus (T2DM) mice via the Irisin/TLR4/MyD88/NF-κB-mediated neuroinflammation pathway, thereby linking anti-inflammatory mechanisms to neurogenesis (91).

Oxidative stress, defined as an imbalance between the production of ROS and the body's antioxidant defenses, has been closely associated with neuroinflammation and impaired neurogenesis in depression (10). Numerous natural compounds exhibit substantial antioxidant activity. For example, Gs-Re has been shown to reduce markers of oxidative stress and inhibit apoptosis (57). Quercetin is well recognized for its potent antioxidant effects (54). Similarly, melanin-like PDA NPs function as effective free-radical scavengers and display marked antioxidative properties (55). Polyphenols, as a class, are known for their antioxidant capacity and have been proposed as a therapeutic strategy for neurodegenerative disorders through the attenuation of oxidative stress (40). Corticosterone disrupts hippocampal neurogenesis and alters behavior through p21-mediated ROS accumulation, suggesting that targeting ROS accumulation may represent a viable therapeutic approach for anxiety disorders, with natural antioxidants potentially contributing to such effects (92). Nb2C MXene-functionalized hydrogels are capable of scavenging ROS, thereby enhancing the proliferation of myoblasts and endothelial cells while promoting neurogenesis (82).

Epigenetic remodeling. Epigenetic modifications, including histone methylation, acetylation, ubiquitination, phosphorylation and lactylation, serve critical roles in the regulation of neurogenesis and the progression of neurodegenerative diseases (93). These modifications can alter gene expression without changing the underlying DNA sequence, thereby influencing the fate, proliferation and differentiation of NSCs. Although direct targeting of epigenetic mechanisms by specific natural compounds in the context of neurogenesis and depression remains an emerging area of research, increasing evidence from the broader field of natural product research has highlighted their potential influence on epigenetic regulation. For example, certain polyphenols have been shown to modulate key epigenetic regulatory enzymes, including histone deacetylases (HDACs) and DNA methyltransferases (DNMTs). As this field continues to develop, additional natural compounds may be identified that exert neurogenic effects, at least in part, through epigenetic remodeling, thereby providing an additional layer of therapeutic intervention.

Mitochondrial bioenergetics. Mitochondrial dysfunction and impaired bioenergetics have been implicated in the pathophysiology of depression and may adversely affect neurogenesis. Proper mitochondrial function is essential for the proliferation, differentiation and survival of NSCs. For example, Gs-Re has been shown to restore mitochondrial membrane potential, a critical determinant of cellular health and function, thereby contributing to its neuroprotective and antidepressant effects (57). Oxidative stress, which is often attenuated by natural compounds, can directly damage mitochondria, leading to energy deficits and disrupted neurogenesis. Therefore, natural medicines that improve mitochondrial function, reduce mitochondrial oxidative stress or enhance cellular energy metabolism may support neurogenesis either directly or indirectly.

Gut-brain axis communication. The gut-brain axis is a bidirectional communication network that links intestinal microbiota, immune signaling, microbial metabolites, neurotransmitter synthesis and brain function. Dysbiosis has been associated with depressive phenotypes and may influence neurogenesis through inflammatory and metabolic mechanisms.

Nicolas *et al* (12) reported that disruption of the gut microbiota in inactive mice impaired hippocampal neurogenesis-dependent tasks and altered behavior in the elevated plus maze. Voluntary exercise mitigated these effects and was accompanied by changes in cecal metabolites, suggesting interactions among the microbiota, physical activity and neurogenesis. Similarly, He *et al* (94) found that restoration of the microbiota following stress rescued stress-induced impairments in hippocampal neurogenesis, supporting a potential role for microbiota-targeted interventions in stress-related depression.

Natural products may also modulate the microbiota-gut-brain axis. Itaconate reduces inflammation, promotes neurogenesis and alters gut microbial composition following anesthesia or surgery (89). Reelin signaling within the enteric nervous system and the microbiota-gut-brain axis has been implicated in depression-related mechanisms, raising the possibility that natural compounds affecting this pathway may indirectly influence neurogenesis (95). Gut microbiota-derived metabolites may therefore contribute to the systemic and central effects of plant-derived compounds (45). However, direct clinical evidence linking microbiota modulation by natural medicines to improved depression outcomes remains limited.

Regulation of autophagy. Autophagy, the cellular process responsible for the degradation and recycling of cellular components, serves a multifaceted role in neurogenesis. While basal autophagy is essential for maintaining cellular homeostasis, its dysregulation can produce detrimental effects. Zhang *et al* (9) demonstrated that excessive neuronal autophagy depletes BDNF and disrupts AHN in a corticosterone-induced mouse model of depression. This hyperactive autophagy, associated with elevated ATG5 expression, leads to lysosomal degradation of BDNF. Importantly, neuronal Atg5 silencing was found to reverse these adverse effects, indicating that neuronal autophagy represents a critical mechanism linking chronic stress to reduced BDNF levels, impaired AHN and depression-like behaviors. Furthermore, Jung *et al* (13) identified that autophagic death of NSCs mediates the decline in AHN and contributes to cognitive impairments associated with chronic stress. Accordingly, natural compounds capable of modulating autophagy, either by preventing its excessive activation or by promoting beneficial autophagic processes, may offer a novel therapeutic strategy for depression through preservation of BDNF levels and support of neurogenesis.

Other regulatory pathways. Numerous additional molecular mechanisms contribute to the complex regulation of neurogenesis and represent potential targets for natural medicines. Notch signaling is recognized as a central regulator of adult neurogenesis, controlling the quiescence, cell cycle entry, and differentiation of NSCs (96). Ephrin receptors (EphRs), essential receptor tyrosine kinases, dynamically influence the fate, migration, morphogenesis, and circuit assembly of NSCs, with dysfunction linked to neurodevelopmental and neurodegenerative disorders (97). Hepcidin deficiency has been shown to impair hippocampal neurogenesis and contribute to brain atrophy and memory decline in murine models, linking iron homeostasis to neurodevelopment and cognitive function (98). Additionally, glucocorticoids, as stress hormones, can modify human cortical neurogenesis by increasing specific populations of basal progenitors, providing a cellular and molecular mechanism for their impact on neurogenesis in humans. Although direct evidence of natural medicines targeting these pathways to restore neurogenesis in depression is still limited, these mechanisms represent promising directions for future research, particularly considering the multi-target potential of many natural compounds.

7. Comparative analysis with conventional antidepressants and emerging therapies

The evidence levels, potential roles and key limitations of these approaches are summarized in Table II (2-4,12,30,54,57, 58,67,76-78,99-113). The treatment landscape for depression continues to evolve, and natural medicines should be considered in the context of established pharmacological, somatic, psychotherapeutic and lifestyle interventions. The objective of such comparisons is to elucidate potential complementary roles, mechanistic overlaps and translational limitations, rather than to suggest equivalence across levels of evidence.

Traditional monoamine antidepressants. Traditional antidepressants, including SSRIs such as escitalopram and SNRIs, primarily act by modulating monoaminergic neurotransmitter systems to alleviate depressive symptoms. While effective for a substantial proportion of patients, a notable subset experiences inadequate treatment response, and therapeutic effects are often delayed, typically requiring weeks to months to reach full efficacy (2). These medications are also associated with various adverse effects, including sexual dysfunction, weight gain, gastrointestinal disturbances and emotional blunting, which can negatively impact adherence and result in treatment discontinuation.

In terms of neurogenesis, conventional antidepressants have been shown in preclinical studies to enhance AHN, suggesting

Table II. Evidence-based comparison of natural medicines, established treatments and emerging interventions for depression.

Therapeutic approach	Mechanistic focus	Evidence level	Potential role	Key limitations/safety issues	(Refs.)
Natural medicines	Multi-target modulation of neurogenesis, inflammation, oxidative stress, gut-brain axis and delivery systems.	Mostly preclinical; selected clinical or human-derived evidence.	Adjunctive or investigational; not a replacement for established care at present.	Standardization, bioavailability, interactions and limited large clinical trials; safety data remain incomplete.	(30,54, 57,58,67)
Conventional antidepressants (SSRIs, SNRIs)	Monoaminergic modulation with downstream neuroplastic effects.	Strong clinical evidence for many patients; neurogenesis links mainly preclinical.	Established first-line pharmacotherapy.	Delayed onset, adverse effects and incomplete remission in a subset of patients.	(2,76,77)
Rapid-acting antidepressants (ketamine, arketamine)	Glutamatergic modulation, NMDA receptor antagonism and rapid synaptic plasticity.	Clinical evidence for severe/TRD settings, with ongoing safety questions.	Rapid intervention under clinical supervision.	Dissociation, abuse potential, monitoring requirements and uncertain long-term safety.	(3)
Electroconvulsive therapy	Network-level neuroplasticity, synaptic remodeling and anti-inflammatory effects.	Established clinical efficacy for severe or treatment-resistant depression.	Severe, urgent or treatment-resistant cases.	Cognitive adverse effects, anesthesia requirements and stigma.	(99-101, 108)
Psychotherapies (CBT, ST, PAT, IPT)	Cognitive, behavioral, interpersonal and schema-level mechanisms; indirect stress and plasticity effects.	Strong clinical evidence across settings.	First-line or adjunctive treatment.	Requires access, adherence, trained therapists and patient engagement.	(2,102-104)
Exercise therapy and bright light therapy	BDNF, exerkines, anti-inflammatory effects and brain connectivity changes.	Clinical and preclinical evidence depending on modality.	Adjunctive lifestyle intervention.	Adherence barriers; may be insufficient alone for severe depression.	(12,78, 105,106, 113)
Neurosteroid replacement (brexanolone)	GABA-A receptor activation and neurosteroid replacement.	Approved for postpartum depression.	Specific indication with rapid symptom relief.	Administration logistics, cost and indication-specific use.	(4)

SSRIs, serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; CBT, cognitive behavioral therapy; ST, schema therapy; PAT, psychoanalytic therapy; IPT, interpersonal therapy; TRD, treatment-resistant depression; BDNF, brain-derived neurotrophic factor.

that this mechanism may contribute to their therapeutic effects (5,6). However, additional research is needed to clarify the extent to which these findings translate to human neurogenesis and the temporal relationship between neurogenic effects and symptom improvement. For instance, a study comparing psilocybin therapy with escitalopram in MDD found that both treatments produced similar personality changes indicative of improved mental health; however, there was no compelling evidence that psilocybin offered a specific advantage over escitalopram regarding personality alterations, and pre-treatment positive expectations for escitalopram influenced post-treatment personality outcomes (77). Moreover, discontinuation of SSRI/SNRI treatment prior to initiating psilocybin therapy may reduce psilocybin's efficacy, highlighting the complex interactions among treatment modalities (76).

Natural medicines often exhibit multi-target mechanisms, modulating neuroinflammation, oxidative stress and neurotrophic signaling in addition to neurotransmitter-related pathways. This polypharmacological profile may hold promise for adjunctive use, although comparative claims are constrained by the current evidence. For example, NHQXW demonstrated antidepressant-like effects comparable to fluoxetine in preclinical models while mitigating withdrawal-related rebound symptoms, suggesting a potentially favorable tolerability profile that requires clinical validation (67). Patient preferences for natural remedies may also influence acceptability and adherence, but such preference data should not be interpreted as evidence of clinical efficacy (107).

Rapidly acting antidepressants. The emergence of rapid-acting antidepressants, such as ketamine and its enantiomer arketamine, has substantially altered the treatment paradigm for severe and TRD. These agents typically produce antidepressant effects within hours to days, in marked contrast to the delayed onset associated with conventional antidepressants. Their mechanisms involve modulation of glutamatergic neurotransmission, particularly through N-methyl-D-aspartic acid receptor antagonism, together with downstream effects on synaptic plasticity and neurotrophic signaling pathways, including BDNF. However, the clinical use of ketamine and arketamine is associated with dissociative adverse effects, abuse potential and the need for careful administration in supervised clinical settings.

Leal *et al* (3) conducted a placebo-controlled pilot study evaluating arketamine as an adjunctive treatment for TRD. In this small-scale study, arketamine did not demonstrate superiority over placebo, although its safety profile was considered acceptable. Larger trials incorporating optimized dosing regimens, repeated administration and parallel-group designs are required. In contrast to the rapid onset of ketamine, most natural medicines exhibit slower and less well-characterized clinical profiles. Advanced delivery systems, such as BDNF-quercetin alginate nanogels, may accelerate therapeutic onset in preclinical models; however, their efficacy and safety in humans require direct evaluation (54).

ECT. ECT remains one of the most effective treatments for severe and TRD, often producing more rapid and pronounced responses than pharmacological interventions. The mechanisms underlying ECT are complex and are thought to involve broad neurobiological changes, including increased hippocampal volume, enhanced neurogenesis and modulation of neuroinflammatory processes.

Deng *et al* (99) investigated the mechanisms of ECT, examining whether its therapeutic effects arise from the seizure itself, the electrical stimulation or a combination of both, while highlighting the rapid efficacy of ECT alongside its potential adverse effect of memory impairment. Evidence suggests that modifications to ECT protocols may improve cognitive outcomes without reducing efficacy; however, their effects on seizure characteristics remain unclear. Abe *et al* (100) provided evidence that ECT-induced increases in hippocampal volume in mice occurred even in animals lacking neurogenesis, indicating that neurogenesis is not required for this specific structural change. Instead, the principal mechanism identified was an increase in excitatory synaptic density within the ventral CA1 region, suggesting that alterations in synaptic architecture, rather than neurogenesis, underlie the observed post-ECT increase in hippocampal volume. This finding challenges previous assumptions regarding the neurogenic basis of ECT-induced structural changes.

Nevertheless, additional studies support the anti-inflammatory effects of ECT. Xu *et al* (101) provided *in vivo* evidence from human subjects demonstrating reduced astrocyte activation and neuroinflammation in individuals with TRD following ECT, using astrocyte-derived extracellular vesicles isolated from plasma samples. Kaurani *et al* (108) reported that baseline levels of microRNA (miR)-223-3p were associated with ECT efficacy. Specifically, responders exhibited downregulation of miR-223-3p together with elevated pro-inflammatory cytokine levels, suggesting that inflammatory markers may have predictive value for treatment response.

Compared with ECT, natural medicines are non-invasive, and some have demonstrated acceptable tolerability in available studies (38,67). However, their efficacy has not been established for severe or TRD, and they should not be regarded as alternatives to ECT in urgent or high-risk clinical situations. A more appropriate interpretation is that selected standardized natural compounds may eventually assume adjunctive or maintenance roles, provided that such applications are supported by robust clinical evidence.

Psychotherapies. Psychotherapies, including cognitive behavioral therapy (CBT), schema therapy (ST), psychoanalytic therapy (PAT) and interpersonal therapy (IPT), are well-established treatments for depression, with evidence suggesting efficacy comparable to pharmacotherapy for certain long-term outcomes (2). These approaches address cognitive distortions, maladaptive behavioral patterns, interpersonal difficulties and underlying psychological schemas.

A comprehensive meta-analysis by Cuijpers *et al* (2), encompassing 409 clinical trials, concluded that CBT produced moderate to large effects relative to control conditions. Importantly, CBT demonstrated greater effectiveness than pharmacological treatments at follow-up assessments conducted 6 to 12 months after treatment and was effective across a range of therapeutic settings. However, evidence supporting its superiority over other psychotherapeutic modalities remains inconclusive.

Several studies have evaluated specific psychotherapeutic approaches. Kopf-Beck *et al* (102) found that supportive therapy (ST) for depression was non-inferior to CBT, although it did not outperform individual supportive therapy. Krakau *et al* (103) reported that adults with chronic depression (103), particularly those with a history of childhood trauma, derived greater long-term benefit from PAT than from CBT over a 5-year period. In addition, Hankin *et al* (104) evaluated brief interpersonal psychotherapy for depression during pregnancy and reported notable improvements in depressive symptoms.

The development of digital health technologies has enabled the implementation of internet-based CBT (i-CBT) and smartphone-delivered CBT, both of which have demonstrated feasibility, acceptability and preliminary efficacy. Some studies have also begun to examine the active therapeutic components of these digital interventions (109-111). Furthermore, algorithm-guided modular psychotherapy has shown potential as a complementary approach to CBT, particularly for patients with depression, psychiatric comorbidities and a history of early trauma (112).

Although psychotherapies do not directly target neurogenesis at the molecular level, their ability to reduce stress, strengthen coping mechanisms and promote positive emotional states may indirectly support conditions favorable to neurogenesis. Natural medicines may serve as adjuncts to psychotherapy by potentially enhancing neuroplasticity and facilitating the cognitive and emotional changes targeted by therapeutic interventions. The combination of natural compounds that promote neurogenesis with psychotherapeutic approaches may therefore produce synergistic effects, potentially improving treatment response and long-term outcomes.

Exercise therapy and bright light therapy (BLT). Exercise therapy has emerged as a well-established intervention for depression, frequently demonstrating improvements in mental health comparable to those of antidepressants, while additionally conferring superior benefits for physical health (105). The underlying mechanisms involve the release of neurotransmitters, neuromodulators, cytokines and neurotrophins, including BDNF, which is critical for supporting neurogenesis (106). Preclinical research indicates that voluntary exercise can counteract gut microbiota-mediated reductions in AHN and associated behaviors in rodent models (12). Moreover, the platelet-derived exerkine CXCL4/PF4, released during physical activity, has been shown to rejuvenate hippocampal neurogenesis and restore cognitive function in aged mice (78). Exercise also promotes hippocampal neurogenesis in T2DM mouse models through the Irisin/TLR4/MyD88/NF-κB-mediated neuroinflammation pathway (91).

BLT is another non-pharmacological approach with demonstrated antidepressant effects. Chen *et al* (113) reported that BLT significantly reduced depressive symptoms and enhanced functional connectivity between the midbrain and frontal cortex in individuals with subthreshold depression, reflecting improved monoaminergic activity and strengthened brain connectivity. Although this study did not directly link BLT to neurogenesis, enhanced monoaminergic tone and frontal-limbic connectivity generally support neuroplasticity.

Natural medicines may complement lifestyle interventions. For instance, dietary polyphenols have been shown in preclinical models to modulate BDNF expression and promote neurogenesis, potentially interacting synergistically with exercise-induced neurogenic effects. The combination of standardized natural compounds with exercise, BLT or other lifestyle-based strategies may therefore provide a multimodal approach; however, these combinations require direct clinical validation.

Neurosteroid replacement therapy. Brexanolone, also known as allopregnanolone, represents a notable advancement in neurosteroid replacement therapy and has received specific approval for the treatment of postpartum depression (PPD). This condition is characterized by neurosteroid withdrawal, and brexanolone, as the first approved therapy of its kind, rapidly alleviates PPD symptoms through activation of GABA-A receptors (4). Its mechanism is distinguished by a rapid onset of action and a unique mode of action while maintaining a tolerable side-effect profile, as it activates both synaptic and extrasynaptic GABA-A receptors. Although the direct effect of brexanolone on neurogenesis is not considered its primary mechanism, neurosteroids generally make important contributions to neuroplasticity and neuronal survival. Natural compounds that modulate neurosteroid-related pathways may warrant investigation as complementary mechanistic leads, although benefits comparable to those of approved neurosteroid therapies have not been established. Investigation of these natural modulators could broaden therapeutic options for conditions such as PPD, in which rapid and targeted interventions are essential.

8. Clinical translation and future directions

The growing body of research on natural therapeutics for depression, particularly those that enhance neurogenesis, provides a promising outlook for future treatment strategies. However, translating these encouraging preclinical findings into widely accepted clinical practices requires overcoming several notable challenges and pursuing focused research directions.

Challenges in clinical translation

Standardization and quality control. A key obstacle in the clinical application of natural medicines is the variability in standardization and quality control. The chemical composition of plant-derived extracts can differ substantially due to factors such as species variation, geographical origin, cultivation practices, harvesting times, processing methods and storage conditions (41,42). This variability complicates the reproducibility of research findings, the determination of optimal dosages, and the assurance of consistent efficacy and safety in clinical use. For complex traditional formulations such as NHQXW, identifying and quantifying all active constituents and their synergistic interactions is particularly difficult (67). Even individual compounds may present challenges related to purity and stability. Without rigorous standardization protocols, including validated analytical methods for active ingredients, broader clinical implementation of natural medicines will remain limited. The development of robust

analytical techniques, such as nanopore analysis for the detection of salvianolic acids in herbal products, is critical to ensure their authenticity and quality (114).

Complex pharmacokinetics and bioavailability. Numerous natural compounds also suffer from poor water solubility, low bioavailability and rapid metabolic degradation, which reduce systemic absorption and limit brain penetration. These limitations often necessitate high doses, increasing the risk of off-target effects or toxicity, and may contribute to inconsistent therapeutic outcomes. The complex pharmacokinetic properties of natural products, especially in multi-component formulations, complicate the prediction of drug-drug interactions and individual patient responses. For example, although quercetin has considerable therapeutic potential, its low oral bioavailability requires advanced delivery systems, such as nanogels, to enhance effectiveness (54). Similarly, *in vivo* evaluation of natural medicines using advanced mass spectrometry data processing is essential for understanding pharmacokinetics and identifying bioactive constituents (56).

Regulatory hurdles and clinical evidence gap. Regulatory frameworks for natural medicines frequently differ from those applied to synthetic pharmaceuticals and are often less standardized across regions. This inconsistency contributes to a perception of reduced scientific credibility. While a number of natural products are marketed as dietary supplements subject to less rigorous regulatory oversight, claims regarding their therapeutic efficacy frequently lack confirmation from robust clinical trials. Therefore, there is a pressing need for large-scale, carefully designed, placebo-controlled, biomarker-stratified clinical trials to validate the efficacy, safety and optimal dosing of natural medicines in the treatment of depression. At present, much of the research is limited to preclinical studies or small pilot trials, which, although valuable for elucidating mechanisms, are insufficient for establishing broad clinical recommendations. This challenge is further compounded by the necessity of integrating traditional knowledge with modern scientific approaches, requiring systematic evaluation of the safety, efficacy and bioactivity of herbal medicines (38).

Opportunities and future directions

Advanced delivery systems and nanotechnology. Nanotechnology offers innovative approaches to overcoming the pharmacokinetic limitations of natural compounds. The development of NDDS, including liposomes, polymeric nanoparticles, micelles and exosome-like vesicles, has the potential to substantially improve the solubility, stability, bioavailability and targeted delivery of natural medicines to the central nervous system (47-53). For example, engineered RVG-BDNF-exosomes and BDNF-quercetin alginate nanogels have demonstrated enhanced brain delivery and therapeutic efficacy in preclinical models. Future research should focus on: i) Developing novel, biocompatible and biodegradable nanocarriers capable of crossing the BBB and delivering natural compounds to specific neurogenic regions; ii) designing intelligent nanocarriers that respond to pathological signals (such as inflammation and oxidative stress) to achieve targeted and controlled release; iii) investigating naturally occurring nanostructures in CHMs, including nanoaggregates and exosome-like vesicles, to exploit their inherent advantages (49,50); and iv) exploring graphene-based nanocomposites in neurogenesis and neuritogenesis, due to their superior electrical conductivity and biocompatibility, to support nerve tissue engineering and promote brain cell regeneration (115).

Biomarker-stratified clinical trials and personalized medicine. To move beyond anecdotal evidence and establish natural medicines as standard therapeutic options, future clinical trials must adopt more rigorous and sophisticated designs. This includes: i) Conducting larger, multicenter, randomized, double-blind, placebo-controlled trials to definitively assess efficacy and safety; ii) incorporating biomarkers of neurogenesis (such as changes in hippocampal volume measured by MRI, blood BDNF levels and performance on neurogenesis-dependent cognitive tasks) to objectively evaluate treatment response and mechanistic involvement in humans; iii) stratifying patients based on genetic predisposition, inflammatory status, gut microbiome composition or specific neurogenic deficits to support personalized medicine approaches and identify subgroups most likely to benefit from treatment; and iv) assessing the long-term efficacy and safety of natural medicines, including their potential to prevent relapse and their effects on overall brain health and cognitive function.

Integration of multi-omics and network pharmacology. Natural medicines are chemically and biologically complex and therefore require integrative analytical approaches to elucidate their mechanisms (2). Multi-omics technologies, including genomics, transcriptomics, proteomics and metabolomics, can link compound exposure to gene expression, protein networks and metabolic pathways (44,45). These approaches may facilitate the identification of biomarkers and treatment-responsive subgroups. In addition, network pharmacology is particularly relevant for multi-component extracts because it characterizes interactions among compounds, targets and pathways (34,35,46). Future studies should emphasize structurally defined analyses and dynamic quantitative network models to improve the identification of lead compounds.

Combination therapy and adjunctive use. Because depression is a multifactorial disorder, natural medicines are unlikely to serve as universal stand-alone treatments. Instead, their multi-target properties may support combination-based therapeutic strategies. Although some natural compounds have demonstrated acceptable tolerability in available studies, their safety profiles still require validation through larger clinical datasets, standardized formulations and careful monitoring for potential interactions. Potential combination strategies include: i) Adjunctive use with conventional antidepressants to enhance treatment response, accelerate onset or reduce selected adverse effects; ii) integration with psychotherapy when neuroplasticity-enhancing effects are hypothesized to facilitate learning and behavioral change; and iii) combination with lifestyle interventions, such as exercise, mindfulness and dietary modification, which may converge on BDNF regulation and neurogenesis (31).

Exploration of new sources and mechanisms. The biodiversity of natural products remains incompletely explored. Future investigations should examine marine organisms, fungi and underutilized medicinal plants as sources of compounds

that modulate neurogenesis. Additional mechanistic studies are also needed to identify novel therapeutic targets. For example, ephrin receptors regulate NSC fate and circuit assembly and may represent druggable targets for natural compounds (97). Similarly, hepcidin deficiency links iron homeostasis to hippocampal neurogenesis and brain atrophy, suggesting a potential avenue for the development of iron-regulating natural products (98).

9. Conclusions

Over the past decade, research has substantially advanced understanding of the relationship between hippocampal neurogenesis and MDD, supporting neurogenesis as an important, although not exclusive, framework for antidepressant development. Studies of natural products have identified plant-derived compounds, traditional formulations and dietary factors that modulate neurogenesis-related pathways, including BDNF/TrkB signaling, microglial activity, oxidative stress and the gut-brain axis. TCM formulations such as NHQXW illustrate the multi-component potential of natural products, although their clinical relevance depends on standardization and controlled clinical trials. Emerging areas, including psilocybin-related neuroplasticity research and nanocarrier-based delivery systems, further expand the translational landscape.

Comparative analyses suggest that natural compounds may complement rather than replace established antidepressant treatments. Their multi-target pharmacology may simultaneously influence multiple biological processes associated with depression; however, evidence regarding clinical efficacy, onset of action and long-term safety remains less robust than that available for established therapies. Although some preparations have demonstrated acceptable tolerability in current studies, broader conclusions regarding safety require larger and longer-term clinical trials. Accordingly, standardized natural medicines should be regarded primarily as adjunctive or investigational approaches until stronger evidence becomes available.

Several challenges continue to limit broad clinical translation. Major barriers include inconsistent product standardization, low or variable bioavailability, complex pharmacokinetic properties, uncertain drug-drug interactions and the need for larger biomarker-stratified clinical trials. Future studies should employ rigorous methodologies, predefined outcome measures and transparent evidence grading while incorporating multi-omics and network pharmacology approaches to clarify mechanisms and identify reliable candidate interventions.

Future research should focus on four priorities: i) Developing advanced delivery systems that enhance the bioavailability and brain targeting of neurogenic natural compounds; ii) conducting large-scale, biomarker-stratified clinical trials to define efficacy, safety, dosing and responsive patient subgroups; iii) integrating multi-omics and network pharmacology approaches to characterize molecular interactions and synergistic mechanisms; and iv) evaluating rational combination strategies involving antidepressants, psychotherapy and lifestyle interventions. Progress in these areas will determine whether natural medicines can become evidence-based components of depression treatment.

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XZ was involved in conceptualization, investigation and writing the original draft. JG was involved in conceptualization and review and editing the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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