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Review Article

Antidepressant Neuroprotective Mechanisms of Natural Products in Depression Management: A Comprehensive Review

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ABSTRACT

Depression is a complex psychiatric disorder with significant global impact. While conventional antidepressants remain the mainstay of treatment, their limitations-such as delayed onset, limited efficacy, and adverse effects-highlight the need for novel approaches. Recent advances include psychedelic-assisted therapy, ketamine infusions, AI-guided precision psychiatry, and neuromodulation techniques, offering more personalized and rapid interventions. Concurrently, Natural Products (NPs) have gained attention for their multi-target neuroprotective effects. Derived from botanical and ethnomedical sources, compounds like apigenin, resveratrol, baicalin, and curcumin modulate neuroinflammation, oxidative stress, neurotransmitter balance, and neuroplasticity. Despite promising preclinical data, challenges such as poor bioavailability, variability in composition, and limited clinical validation hinder their integration into mainstream care. This review explores the evolving landscape of depression management, emphasizing the therapeutic potential and translational challenges of NPs as adjunct or alternative treatments in addressing unmet clinical needs.

Keywords: Natural Products, Depression, Neuroprotective Mechanism.

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INTRODUCTION

Depression is a common mental illness constitutes a critical public health burden which affecting over 322 million individuals, approximately 3.8% of the global population. It enhances the of socioeconomic burden to patients through profound disability, diminished quality of life and elevated healthcare cost (Chodavadia *et al*., 2023). According to the World Health Organisation 2023, Major Depressive Disorders (MDD) is a single largest contributor to global disability causes 50.6 million Disability Adjusted Life Years (DALYS) associated with economic losses exceeding $1 trillion annually. In the United States, in 2021, the prevalence reaches 8.4% (21 million adults) with 18.7% of adolescents affected. Globally female experience 1.7 folds higher rates than males (Chodavadia *et al*., 2023; National Institute of Mental Health, 2021).

Depression leads to cognitive deficits, including impaired memory and executive function, with neuroimaging showing reduced activity in prefrontal and hippocampal regions. Its pathology extends beyond monoamine deficiencies to include HPA axis and GABAergic dysregulation, persistent inflammation, and disrupted neuroplasticity, resulting in neurochemical imbalances, neuronal damage, and structural brain changes that contribute to depressive symptoms and disease progression (Rădulescu *et al*., 2021).

Current first-line pharmacotherapies include Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) along with older Tricyclic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs). However, these therapies have significant limitations include delayed therapeutic onset (often exceeding two weeks), suboptimal efficacy in majority of cases, intolerance and serious adverse effects that frequently compromise patient adherence. This inadequacy therapy underscores an urgent demand for novel, effective and better tolerated therapy to reduce socio-economic burden (Elena Dale a *et al*., 2015).

Natural Products (NPs) sourced from botanical, fungal, marine and ethnomedical traditions may offer long-term promising therapeutic avenue due to their historical utilization, chemical diversity and inherent capacity for multi-target engagement. Crucially, expanding preclinical and emerging clinical research highlights their neuroprotective properties as key mechanism of

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relevant to depression (Wainwright *et al*., 2022). NPs demonstrate the ability to modulate the core pathological pathways through mitigating neuroinflammation, reducing oxidative stress burden, normalizing HPA axis hyperactivity, potentiating neurotrophic factor signalling, stimulating neurogenesis and synaptic plasticity, and restoring GABAergic/glutamatergic equilibrium (Vaou *et al*., 2025).

All things considered, more new and efficient research on major depressive disorder treatment is desperately needed. The pharmaceutical industry and scientific community are paying attention to natural substances because they can lessen the symptoms of several illnesses, including depression (Cui *et al*., 2024). In this study aims to review the relevant mechanisms and the possible application of natural substances in the treatment of depression. The antidepressant potency of specific NPs varies based on their actions on neurochemicals, different parts of neurons, HPA axis and GABAergic/glutamatergic neurotransmitter signalling. Despite of potential therapeutic effects, the clinical translation of NPs is hindered by challenges such as variability in phytochemical composition, poor bioavailability, insufficient long-term evidence, possible herb-drug interactions and absence of harmonized regulatory standards for clinical use. Effective utilization of NPs for depression necessitates a critical unmet need as the depression remains global crisis with substantial therapeutic gaps. To evaluate the therapeutic promises of NPs, this review aimed to find the evidences of NPs that propose their neuroprotective mechanisms against depression.

ETIOLOGY AND PATHOPHYSIOLOGICAL MECHANISMS TO INDUCE DEPRESSION

Depression is a debilitating multifactorial psychiatric illness characterized by persistent low mood, cognitive deficits and neurodegeneration. The aetiology arises from complex interplay of genetic vulnerability, epigenetic modifications, environmental stress and dysregulation across neurobiological, neuroendocrine, immune and metabolic systems (Duman *et al*., 2019). Contemporary understanding has moved significantly beyond the monoamine hypothesis recognising depression as a disorder of neural circuit plasticity and resilience. This is driven by converging pathological mechanism that induce neuronal damage, synaptic loss and network dysfunction. Understanding these mechanisms is paramount for identifying targets where neuroprotective natural products may exert therapeutic benefits. This section describes the primary etiology pathways implicated in depression pathogenesis (Figure 1) (Beurel *et al*., 2020; McEwen and Akil, 2020).

Genetic predisposition and epigenetic regulation

It has been estimated that 30-40% of depression is heritable with genome wide associated with the identifying numbers susceptibility 66 genetic loci (Howard *et al*., 2019). Major genes implicated include those regulating neurotransmitter systems (SLC6A4 - serotonin transporter, COMT - catechol-O-methyltransferase), neurotrophic signalling (BDNF - brain derived neurotrophic factor), stress response (FKBP5 - immunophilin regulating Glucocorticoid Receptor (GR) sensitivity; CRHRI - corticotropin releasing hormone receptor 1) and synaptic function (GRIA2, GRIN2A - glutamate receptors) (Cathomas *et al*., 2019). Critically, these genetic risks interact with environment through epigenetic mechanism. Early life adversity and chronic stress induce persistent alterations in DNA methylation and hippocampus supressing GR gene (hypermethylation of NR3C1) altering HPA axis feedback. Further, histone modification (reduced H3K27ac at synaptic gene promoters) and non-coding RNA expression (dysregulation of miR-124, miR132, MiR218 targeting CREB and BDNF signalling) (Nestler *et al*., 2015). These epigenetic modification act as molecular scars, silencing neuroplasticity genes, amplifying stress reactivity, priming inflammatory responses and establishing enduring biological vulnerability (Turecki and Meaney, 2016).

Neurological dysregulations: synaptic plasticity and neurotransmission

Chronic stress and underlying pathophysiological process converge to impair synaptic plasticity and disrupt neurotransmission beyond monoamines. Chronic stress and inflammation impair astrocytic glutamate reuptake via downregulation of excitatory amino acid transporters (EAAT1/2) leading to synaptic and extra synaptic glutamate excess (Popoli *et al*., 2012). Activation of extra synaptic containing GluN2B containing NMDA receptors triggers calcium influx activating enzymes link nNOS and calpains culminating in dendritic atrophy, spine loss and impaired long-term potentiation in hippocampus, prefrontal cortex and nucleus accumbent. Collapse of neurotrophic support system most notably involving in reduction of BDNF signalling through its receptor TrkB (Gerhard *et al*., 2016). Diminished BDNF impairs neuronal survival, dendritic complexity, hippocampal neurogenesis and synaptic efficacy. Deficits in VEGF and IGH-1 further compromise neurovascular coupling and cellular resilience. GABAergic dysfunction particularly reduces function of parvalbumin positive interneurons in corticolimbic circuits which contributes to disrupted network oscillation and impaired inhibitory control over emotional processing. These insults create a state of impaired neuroplasticity and cellular vulnerability (Gerhard *et al*., 2020).

Neuroinflammation, oxidative stress and mitochondrial impairment

Chronic low-grade inflammatory state is a core feature of a significant depression subset. Peripheral immune activation due to stress, obesity, infection and dysbiosis increases pro-inflammatory cytokines (IL-1, IL-6, TNF-αand CRP) (Miller and Raison, 2016). These signals access the brain via active transport compromised

Blood Brain Barrier (BBB) or vagal afferents activating microglia and astrocytes. Activated microglia adopt a pro-inflammatory (M1) phenotype releasing more cytokines, chemokines and Reactive Oxygen Species (ROS). Cytokines induce Indoleamine 2,3-Dioxygenase (IDO) shifting tryptophan metabolism away from serotonin synthesis towards the kynurenine pathway. Concurrently, inflammation and stress generate overwhelming oxidative stress deplete antioxidants (glutathione and superoxide dismutase) and causing lipid peroxidation, protein carbonylation and DNA damage (Black *et al*., 2015). Mitochondrial dysfunction is a critical amplifier that promoted through impaired Electron Transport Chain (ETC) function, reduce ATP production, increased mitochondrial ROS (mtROS) and disrupted calcium buffering lead to bioenergetic failure. mtROS and released Mitochondrial DNA (mtDNA) act as DAMPs activating the NLRP3 inflammasome which process pro-IL-1 β into its active form creating a vicious cycle of inflammation and cellular damage (Kaufmann *et al*., 2017).

Hypothalamic Pituitary Adrenal (HPA) axis dysfunction

Chronic hyperactivity and impaired negative feedback of the HPA axis are central to depression pathophysiology. Chronic stress elevates Corticotropin Releasing Hormone (CRH) and Arginine Vasopressin (AVP) in the hypothalamus increasing Adrenocorticotropic Hormone (ACTH) release and ultimately cortisol (Juruena *et al*., 2018). Glucocorticoid resistance often linked to FKBP5 polymorphisms and NR3C1 epigenetic modification prevents cortisol from effectively suppressing CRH/AVP and CTH release via negative feedback mechanism (Zannas and Binder, 2014). Excess glucocorticoids exert neurotoxic effects that suppress BDNF expression led to reduction of hippocampal neurogenesis. This promotes dendritic atrophy in the PFS and hippocampus enhancing glutamatergic transmission, activating microglia, impairing BBB integrity and inducing mitochondrial dysfunction and oxidative stress (Picard and McEwen, 2018). Glucocorticosteroids also potentiate inflammatory response by enhancing cytokine signalling and impairing anti-inflammatory pathways. Conversely, the pro-inflammatory cytokines (IL-1β and TNF-α) can directly impair GR function and signalling that creating self-amplifying loop between neuroendocrine and immune dysfunction that drives neuronal damages (Pariante, 2017).

Structural and functional neural circuit alterations

The preceding mechanisms manifest in measurable brain changes. Structural MRI studies consistently show reduced volumes in the hippocampus, prefrontal cortex, Anterior Cingulate Cortex (ACC) and insula which reflecting dendritic atrophy, synaptic loss, reduced neurogenesis and glial pathology (Schmaal *et al*., 2016). Functional MRI reveals complex circuit dysfunctions specially hyperactivity and hyperconnectivity in limbic region (amygdala, subgenual ACC and insula) mediating threat deletion and negative effects. Disrupted connectivity within and between large scale networks essentially alter the cognitive control and emotion regulation. Major alterations include increased Default Mode Network (DMN) connectivity decrease Central Executive Network (CEN) connectivity and weakened CEN control over the Salience Network (SN) and DMN (Tozzi *et al*., 2020). These changes underlines core symptoms include persistent negative effects, anhedonia, executive deficits and rumination. The mechanisms deriving this remodelling involve synergistic actions of glucocorticoids, inflammation, oxidative stress and reduced neurotrophins on synaptic plasticity, neurogenesis, gliogenesis and white matter integrity (Mulders *et al*., 2015).

Gut-brain axis dysbiosis and microbial signalling

Patients with depression exhibit gut dysbiosis that reduce overall diversity, decreased beneficial bacteria (Faecalibacterium, Lactobacillus, Bifidobacterium and Roseburia) and increased pro-inflammatory taxa (Simpson *et al*., 2021). This dysbiosis compromises intestinal barrier integrity (leaky gut) permitting translocation of bacterial Lipopolysaccharide (LPS) and other microbial products. LPS activates peripheral immune cells and brain endothelial Toll Like Receptor 4 (TLR4), triggering systemic and neuroinflammation (Kelly *et al*., 2016). Gut microbiota significantly influences tryptophan metabolism, favouring the kynurenine pathway over serotonin synthesis. Microbial metabolites, particularly Short Chain Fatty Acids (SCFAs) like butyrate, propionate and acetate that exert potent neuroactive effects. Butyrate is an HDAC inhibitor that promotes histone acetylation, enhancing BDNF expression and neurogenesis (Silva *et al*., 2020).

Environmental triggers

Biological vulnerabilities are activated and exacerbated by environmental factors acting across the lifespan. Early Life Adversity (ELA) is major risk factor including persistent epigenetic reprogramming (BDNF, NR3C1 methylation), HPA axis hyper-reactivity, chronic inflammation and structural brain changes (Teicher and Samson, 2016). Chronic psychosocial stress un adulthood (work stress, poverty, caregiving and social isolation) perpetuates dysregulations leading to allostatic overload. The cumulative physiological burden from maladaptive stress responses. Subsequently, it induced accelerated cellular aging, increased oxidative stress, metabolic dysfunction, persistent inflammation and neuronal dagame (Lindqvist *et al*., 2015). Circadian disruption dysregulates glucocorticoid rhythms, monoamine turnover, immune function and mitochondrial metabolism. Environmental toxins, poor diet, physical inactivity and sleep deprivation compound these risks. Global stressors like the COVID-19 pandemic exacerbate depression through sustained uncertainty, fear, isolation and grief acting via heightened neuroinflammation, HPA axis activation and

amygdala sensitization (Slavich and Sacher, 2019). These factors exploit genetic and epigenetic susceptibilities overwhelming neuroprotective capacities and disrupting neuroimmune endocrine metabolic homeostasis.

CURRENT TREATMENT/CONVENTIONAL TREATMENT APPROACHES FOR DEPRESSION MANAGEMENT

Pharmacotherapy: targeting neurochemical and plasticity pathways

Conventional antidepressant pharmacotherapy primarily modulates monoaminergic systems, yet its therapeutic effects depend critically on downstream neuroplastic adaptations rather than acute neurotransmitter changes. The Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) inhibits presynaptic serotonin transporter and norepinephrine transporters result in synaptic monoamine availability (Malhi and Mann, 2018). They required 2-8 weeks therapeutic lag reflects the time required for neurotrophic and synaptic reorganization rather than immediate neurotransmitter effects (Castrén and Monteggia, 2021). Chronic administration upregulates Brain Derived Neurotrophic Factor (BDNF) signaling through TrkB receptors that promote dendritic spine formation and hippocampal neurogenesis via mTOR pathway activation (Duman *et al*., 2016). This process involves epigenetic modifications include histone acetylation at BDNF gene promotors which reverse the stress induced neuronal atrophy in prefrontal cortex. The discovery of rapid acting agents like ketamine demonstrated that NMDA receptor blockade on GABergic interneurons triggers a glutamate surge by acting on BDNF-TrkB-mTOR cascades to restore synaptic connectivity within 24 hr (Zanos, 2017). Similarly, neurosteroids like zuranolone enhance inhibitory tone through δ-subunit containing GABA-A receptors that normalizing HPA axis hyperactivity in postpartum depression (Cipriani *et al*., 2018). Despite these advances these therapy persist significant limitation such as only 40-60% of patient achieve remission with first-line agents (Tansey *et al*., 2014). Treatment resistance correlates strongly with baseline inflammation (hsCRP>3 mg/L) and low BDNF (Short *et al*., 2018). Most of the agents lack of direct effects on mitochondrial dysfunction or oxidative stress pathways. Ketamine poses transient efficacy (median duration 7 days) and discontinuation increase further risks of unmet therapeutic needs (Månsson *et al*., 2016).

Psychotherapy: circuit targeted neuroplasticity

Evidence base psychotherapies remodel neural circuits through structured cognitive and behavioral interventions. Cognitive Behavioral Therapy (CBT) is the most empirically validated modality that reduces pathological rumination by weakening default mode network hyperconnectivity while strengthening functional coupling between the dorsolateral prefrontal cortex and amygdala. Neuroimaging studies confirm consistent reductions in amygdala reactivity and 3-5% hippocampal volume increases following 12-16 sessions mediated by cortisol normalization and BDNF elevation (Gotink *et al*., 2016). Mindfulness Based Cognitive Therapy (MBCT) achieves comparable effects through attentional control training that increases gray matter density in the anterior cingulate cortex reducing amygdala reactivity by 27% in remitted patients (Roberts *et al*., 2015). Both modalities induce beneficial epigenetic changes through CBT demonstrably alters FKBP5 methylation patters to enhance glucocorticoid receptor sensitivity. However, efficacy requires preserved cognitive capacity (MoCA>26) limit utility in severe melancholic depression (da Sliva. *et al*., 2018). Crucially, neither modality significantly reduces peripheral inflammatory cytokines or oxidative stress biomarkers reflecting limited impact on fundamental cellular pathologies. Significant accessibility barriers include therapist shortages, high costs and high dropout rates (Njau *et al*., 2017).

Neuromodulation: direct intervention with neural circuits

Neuromodulation techniques provide rapid intervention for Treatment of Resistant Depression (TRD). Electroconvulsive Therapy (ECT) is the most effective option for severe TRD that induces an acute neurotrophic surge with Vascular Endothelial Growth Factor (VEGF) increases significantly. This reverses hippocampal atrophy but simultaneously triggers dentate gyrus expansion that correlates with retrograde amnesia (Argyelan *et al*., 2019). ECT also normalizes pathological hyperconnectivity in the subgenual anterior cingulate cortex through GABAergic interneuron proliferation (Blumberger *et al*., 2018). Modern protocols like intermittent Theta-Burst Stimulation (iTBS) achieve comparable higher remission rate through efficient long term potentiation induction of magnetic plus that activate voltage gated calcium channels, triggering CAMKII/ERK phosphorylation to strengthen prefrontal limbic synapses. Standard high frequency rTMS (10Hz) to the left dorsolateral prefrontal cortex modulates attention networks while increasing GABA-A receptor density that confirmed by magnetic resonance spectroscopy studies (Dubin *et al*., 2016). Practical limitations include ECR process require anesthesia and persistent cognitive concerns. rTMS is an intensive 4-6-week daily session. These approach neither adequately addresses peripheral inflammation or mitochondria dysfunction (Teicher and Samson, 2016).

Adjunctive strategies: targeting inflammation and gut-brain signaling

Augmentation approaches address specific pathophysiological pathways. Lithium remains a cornerstone for TRD management by inhibiting Glycogen Synthase Kinase-3β (GSK-3β) which enhances mitochondrial biogenesis via PGS-1α activation and upregulating neuroprotective Bc1-2 (Köhler *et al*., 2014).

Anti-inflammatory strategies show promise in biomarker selected patients such as celecoxib augmentation doubles SSRI response rates in high inflammation level of depression (hsCRP>5 mg/L) by suppressing prostaglandin E_2 medicated microglial activation while minocycline reduces ventral striatal glutamate/GABA imbalances through inhibition of NOX2 derived oxidative stress (Ho *et al*., 2021). Gut-brain axis interventions demonstrate clinical potential and faecal microbiota transplantation achieves highest rate of symptom reduction in TRD by restoring butyrate production and reduces neurotoxic quinolinic acid (Xie *et al*., 2021). However, lithium is narrow therapeutic index necessitates rigorous blood monitoring, anti-inflammatory agents exhibit poor blood brain barrier penetration and microbiome therapies due to lack of standardized protocols (Sanada *et al*., 2020).

Critical neuroprotective deficits in current paradigms

Conventional therapies collectively fail to address core aspects of depression neuropathology. Mitochondrial dysfunction related to impaired electron transport chain complexes remain unmodified by existing treatments (Scaini *et al*., 2022). Oxidative stress markers show no normalization post therapy, perpetuating neuronal vulnerability (Black *et al*., 2015). The blood brain barrier excludes virtually all anti-cytokine biologics and many antioxidants while childhood trauma induced epigenetic scars persist symptomatic remission (Lakhani *et al*., 2019). These limitations are particularly determinant in inflammation associated and early life stress subtypes where peripheral medicators continuously prime microglial activation and oxidative damage (Ménard *et al*., 2017). The therapeutic lag of conventional antidepressants reflects this mechanistic incompleteness as neuron remain susceptible to excitotoxicity during the weeks mechanistic incompleteness. Neuron remain susceptible to excitotoxicity during the weeks required for neuroplastic adaptions to manifest (Liu *et al*., 2017).

NEW APPROACHES IN MANAGEMENT OF DEPRESSION

In recent years, the management of depression has undergone a transformative shift, embracing a more personalized, neurobiologically informed, and integrative approach (Figure 2). Psychedelic-assisted therapies, such as psilocybin and MDMA, are now clinically used for treatment-resistant depression and PTSD. When combined with psychotherapy, these approaches show remarkable effectiveness, with MDMA therapy leading to 88% remission in severe PTSD and psilocybin plus CBT providing 40% greater symptom improvement than CBT alone (Barber and Aaronson, 2022).

Another major advancement is the refinement of ketamine therapy that evolved from hospital-based infusions to at-home treatment protocols under remote clinical supervision. Ketamine is known for its rapid-acting antidepressant effects and now administered in carefully monitored regimens that balance efficacy with safety. A recent clinical trial reported an 80% remission rate in PTSD following six ketamine infusions over two weeks. These therapies are particularly valuable for individuals who have not responded to conventional antidepressants or psychotherapy (Yavi *et al*., 2022).

In parallel, the integration of Artificial Intelligence (AI) into mental health care has enabled the development of precision psychiatry where treatment plans are tailored to individual profiles based on genetic, neurobiological and psychosocial data. AI-driven platforms can now predict treatment responses, optimize medication selection and dynamically adjust therapeutic strategies, thereby improving outcomes and reducing trial-and-error prescribing (Cruz-Gonzalez *et al*., 2025).

Additionally, Multifamily Therapy (MFT) has gained traction as a community-based intervention for Difficult-to-Treat Depression (DTD). By involving multiple families in a shared therapeutic environment, MFT fosters collective resilience that enhances treatment adherence, and provides a robust support network, particularly for patients with complex trauma histories or comorbid substance use disorders (Paganin, 2024).

Complementing these innovations is a growing emphasis on holistic and integrative care models that address the biopsychosocial dimensions of depression. These models incorporate lifestyle interventions such as structured physical activity, nutritional psychiatry, sleep optimization and mindfulness-based practices into standard treatment protocols. This comprehensive approach not only targets symptom reduction but also promotes long-term recovery and relapse prevention (Marx *et al*., 2023).

Finally, advances in neurostimulation techniques including Transcranial Magnetic Stimulation (TMS) and modernized Electroconvulsive Therapy (ECT) have improved the safety and precision of these modalities. ECT stigmatized is now used with refined protocols that minimize cognitive side effects and is reserved for severe drug-resistant cases with bipolar features. Together, these emerging strategies represent a paradigm shift in depression management moving from a one-size-fits-all model to a personalized, multimodal and evidence-based framework that holds promise for more effective and enduring treatment outcomes (Mukhtar *et al*., 2023).

ROLE OF NATURAL PRODUCTS IN DEPRESSION MANAGEMENT

Natural products have been explored for depression management due to their unique mechanisms and potential safety advantages. Plant-based agents may influence stress, mood, endocrine, and immune responses, supporting mental well-being and resilience. Research suggests such compounds can complement conventional treatments, addressing both psychological and physiological aspects of depression.

Flavonoid Apigenin

The flavonoid apigenin (4,5,7-trihydroxy flavone) is primarily found in citrus fruits, spinach, chamomile, limes, and apples (L. Zhu *et al*., 2023). Studies associate apigenin with antioxidant, anti-cancer and anti-inflammatory properties. It has also been examined for its influence on depressive-like behaviours via modulation of pathways such as PI3K/Akt and p38/MAPK, γ-receptor expression and serum BDNF levels (Sharma *et al*., 2019). In animal models, doses of apigenin have been observed to increase hippocampal BDNF and decrease inflammatory markers possibly contributing to antidepressant effects (Al-Yamani *et al*., 2022).

Resveratrol

The resveratrol is a phenolic compound present in red wine, grapes, peanuts, cocoa powder and pasta that has been studied for its possible antidepressant properties. Clinical trials involving oral doses of resveratrol (500 mg over 13 weeks) have measured its concentration in cerebral fluid (Hurley *et al*., 2014). Although about 70% of orally administered resveratrol is absorbed, hepatic metabolism reduces its bioavailability to around 0.5%. Buccal administration has been proposed as an alternative delivery method. After holding 1 mg of resveratrol in the mouth then plasma concentrations reached 37 ng/mL within two minutes which may require intake of 250 mg via tablets (Shukla *et al*., 2024). Research supports its neuroprotective and anti-inflammatory effects. In rodent studies, resveratrol appears to affect the absorption of monoamines such as serotonin and noradrenaline as well as monoamine oxidase activity. Increased levels of certain neurotransmitters and reduction in depression-like behaviors have been documented that suggesting interaction with the monoaminergic system (Shen *et al*., 2020).

Baicalin

Baicalin is a flavonoid component purified from the roots of *Scutellaria baicalensis*. It has been attributed with antioxidant, anti-inflammatory, and neuroprotective actions (Jia *et al*., 2021). Animal models indicate baicalin can modulate neurogenesis and synaptic plasticity and it has been studied for antidepressant-like effects particularly in chronic unpredictable mild stress paradigms. Mechanistically, baicalin has been shown to regulate pathways such as AMPK and PI3K influence synaptophysin, Rac1-cofilin, TrkB receptor expression. Other studies highlight its ability to inhibit GSK3β/NF-κB/NLRP3 pathways reduce learning and memory impairment following ischemia/reperfusion and alter inflammation-related cytokines (Zheng *et al*., 2015). Baicalin also impacts Wnt/β-catenin signalling associated with hippocampal neurogenesis that reversing stress-induced disruptions of this pathway and influencing gene expression related to neural growth (Lu *et al*., 2019).

Berberine

Berberine is a natural alkaloid found in plants like Oregon and European grapes, is used in herbal therapy for mood disorders. It demonstrates antioxidant properties by inhibiting pro-oxidant enzymes (Neag *et al*., 2018), and exhibits neuroprotective and antidepressant effects by regulating neurotransmitters and increasing Brain-Derived Neurotrophic Factor (BDNF) expression (B. Lee *et al*., 2012). Berberine's benefits involve modulating the hippocampal BDNF-eEF2 pathway, cAMP-CREB signalling and specific microRNAs promoting neurogenesis and reducing depressive behaviors (Zhan *et al*., 2021). Additionally, it decreases NLRP3 inflammasome-mediated inflammation and preserves synaptic plasticity to contribute in antidepressant action.

Saffron

Saffron from *Crocus sativus* L., shows promise as a treatment for depression due to active compounds like safranal and crocin which affect serotonin, dopamine and norepinephrine pathways (Bukhari *et al*., 2018). These constituents act as antioxidants, anti-inflammatories, and may modulate HPA axis activity and BDNF expression (Taheri-Amlashi *et al*., 2022). Animal studies indicate saffron influences neurotransmitter levels, immune response and oxidative stress. This reduces depressive and compulsive behaviours (Scuto *et al*., 2022). Clinical research also notes significant improvements in depressive symptoms after saffron supplementation (Kell *et al*., 2017).

Folic Acid (Vitamin B)

It is a water-soluble nutrient found in vegetables like spinach and kale, and fruits such as papaya, broccoli, banana, mango, kiwi and pomegranate which are often deficient in people with depression (Rosa *et al*., 2014). Supplementing with folic acid can prevent and treat folate deficiencies and may help reduce the risk of neurological disorders like depression by supporting monoamine neurotransmitter production (De Long *et al*., 2014). Low folic acid levels are linked to decreased dopamine, norepinephrine and serotonin which may contribute to depression. Studies show depressed individuals have lower serum folic acid and consume less folate than healthy controls (Bender *et al*., 2017). Folic acid supplementation helps restore beta cell function and normalizes neurotransmitter levels, inhibits inflammation, and regulates molecules including homocysteine, BDNF and β-endorphin (Budni *et al*., 2021).

Genipin

The genipin is an iridoid compound from *Gardenia jasminoides* that exhibits potential antidepressant effects via multiple mechanisms affecting mood regulation, neuroplasticity, inflammation and cellular health. Genipin is produced in the body from geniposide and has shown efficacy in animal models for depression (Cai *et al*., 2015). It possesses antioxidant,

anti-inflammatory, antithrombotic, anti-diabetic, neuroprotective and anti-tumour properties, and modulates epinephrine and serotonin in the hippocampus (Y. Wang *et al*., 2017). Genipin likely influences post-receptor signalling of the monoaminergic system and BDNF levels. Studies report its effectiveness in reducing depression-related behaviours in mice and elevating 5-HT and noradrenaline similar to antidepressants, along with regulating BDNF (J. Wang *et al*., 2016).

Curcumin

It is obtained from *Curcuma longa*, has attracted interest for its potential in treating depression, though its poor bioavailability due to rapid metabolism and low absorption remains a challenge. Strategies such as using analogues, liposomes or nanomaterials are being explored to improve this. Animal studies demonstrate curcumin's anti-depressant effects showing improved behaviour and neurochemical changes linked to serotonin, dopamine and noradrenaline regulation. Co-administration with certain antidepressants can enhance these effects, possibly by increasing hippocampal BDNF and engaging specific 5-HT receptors (Kaufmann *et al*., 2016).

Genistein

It is a soybean-derived isoflavone, shows effectiveness in managing depression, osteoporosis, cardiovascular disease and cancer. Studies report that genistein improves quality of life and reduces depressive symptoms particularly in postmenopausal women (Kageyama *et al*., 2010). Its anti-depressant action may involve modulation of the 5-HT1A receptor and MAO inhibition. Long-term treatment in animals yields similar benefits to standard antidepressants (Atteritano *et al*., 2014).

Carvacrol

It is a monoterpene phenol from oregano and thyme that exhibits anti-inflammatory, analgesic, anti-arthritic, anti-carcinogenic, anti-diabetic, cardioprotective, gastroprotective, hepatoprotective and neuroprotective properties (Melo *et al*., 2011). It acts by modulating human ion channel receptors, stimulating PPARs and inhibiting COX2-mediated inflammation (Rathod *et al*., 2021).

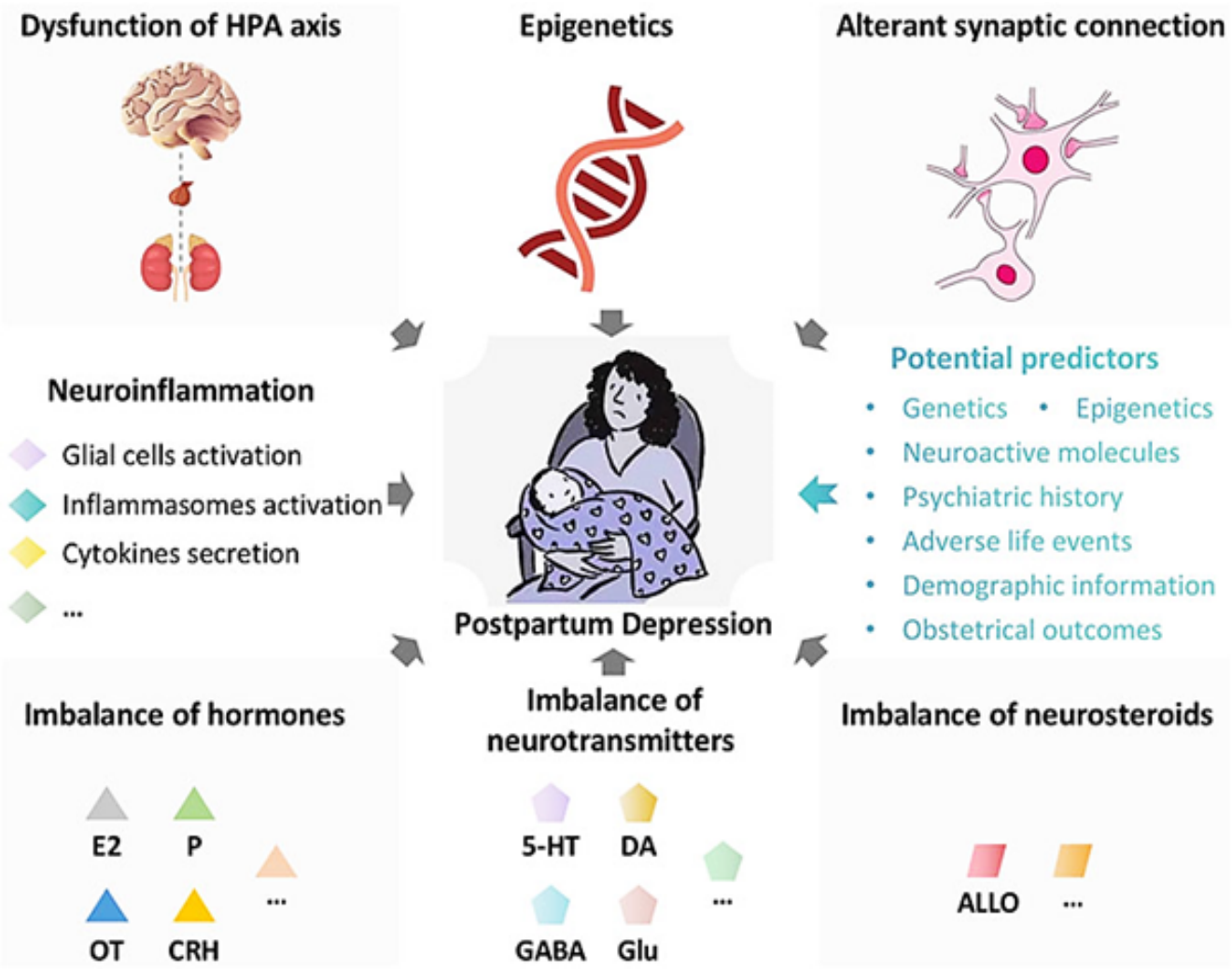

Figure 1: Possible etiology and pathophysiology associated with depression. The figure is adapted from Zhu *et al*. (2022).(J. Zhu *et al*., 2022)

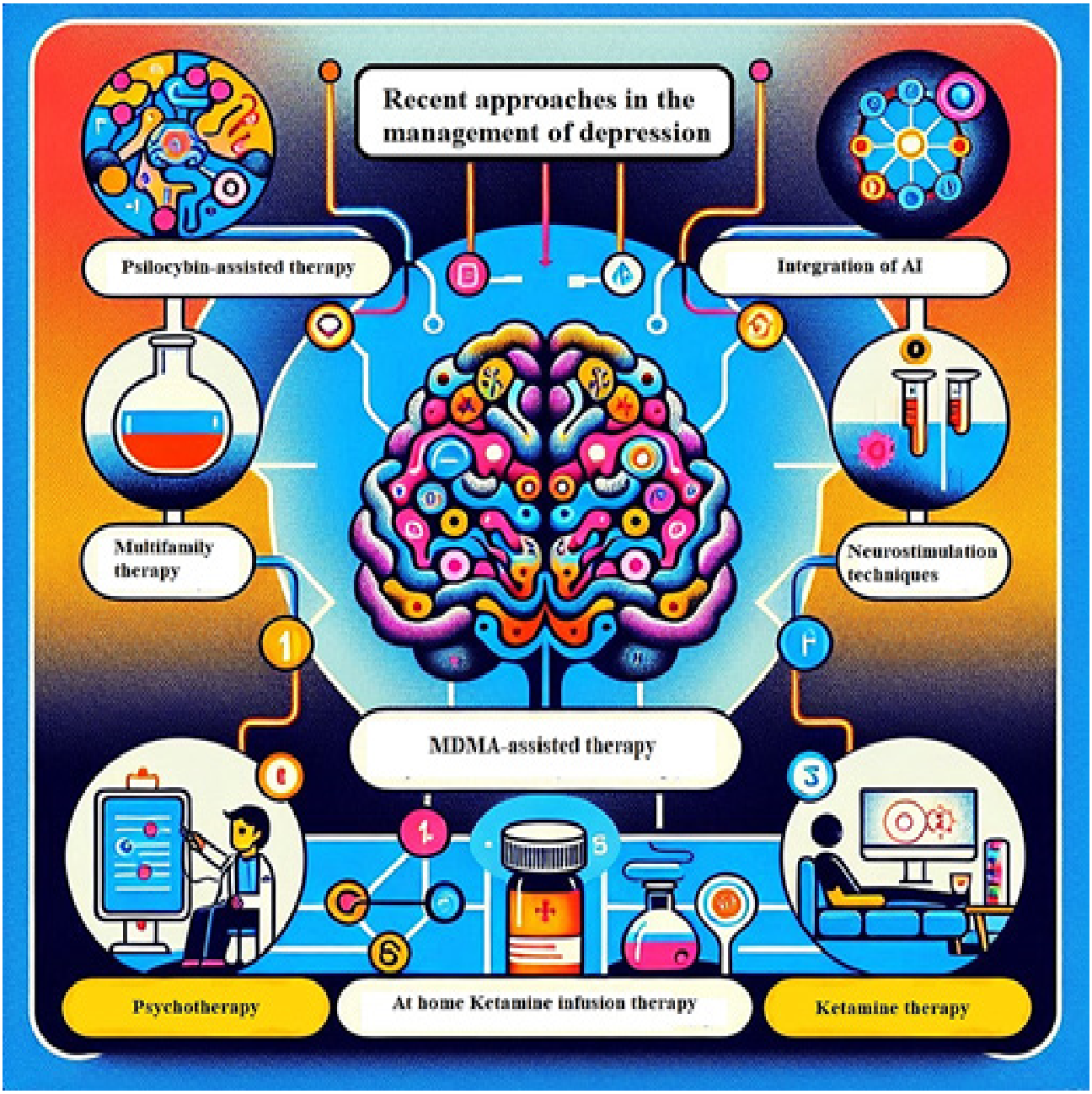

Figure 2: A illustrate for the recent and new approaches for the management of depression.

CYP2A6 is the main enzyme metabolizing carvacrol, which may interact with other drugs processed by this pathway (Dong *et al*., 2012). Oral doses (12.5-50 mg/kg) show anti-depressant effects in rats likely via dopaminergic pathways and increased 5-HT and dopamine in key brain regions (Zotti *et al*., 2013).

Piperine

It is an alkaloid in long and black pepper that has anti-depressant potential by increasing BDNF expression and monoamine neurotransmitter levels while reducing MAO activity in rodent models (Mao *et al*., 2014). It also regulates serotonin systems, lowers oxidative stress, protects PC12 cells from corticosterone toxicity and supports neuroprotection and anti-inflammation, all contributing to its anti-depressant effects (Vaibhav *et al*., 2012).

Luteolin

The luteolin is a flavonoid found in plants like celery, green pepper, green leaves and perilla seeds that readily crosses into the brain and offers anti-inflammatory, anti-anxiety and memory-enhancing effects. It acts as an antioxidant, deactivating nitrogen and oxygen species which may help treat neurological conditions linked to oxidative stress and neuroinflammation (Gupta *et al*., 2018). Luteolin also limits NF-κβ and TLR4 signalling which reduces cytokine production. This shows BDNF-like activity by reducing microglial activation (Ishisaka

et al., 2011). Additionally, it suppresses NO and PGE2 synthesis led to inhibits LPS-induced activation of iNOS, COX-2, TNF-α, IL-1β and NF-κβ (J. K. Lee *et al*., 2009).

Quercetin

It is a polyphenol present in strawberries, apples, grapes, broccoli, tea and citrus fruits that has anti-inflammatory, antiviral, antiallergic and antirheumatic properties (Bhutada *et al*., 2010). Studies show quercetin improves memory, reduces stress, anxiety and depression in animal models by modulating BDNF and iNOS, and altering neurochemical pathways (Samad *et al*., 2018).

Naringenin

It is a flavonoid present in plants like *Solanum lycopersicum*, citrus fruits and others shows anti-depressant properties by regulating brain serotonin and noradrenaline levels and reversing HPA axis dysfunction (Legeay *et al*., 2015; Yi *et al*., 2012). It may alleviate depression through antioxidant activity and inhibition of monoamine oxidase. Animal studies show that naringenin's antidepressant-like effects involve modulating neurochemical and neuroendocrine activity, increasing hippocampal glutathione reductase which boosting monoamine neurotransmitters and lowering serum corticosterone (Bansal *et al*., 2018). It enhances antioxidant enzymes, reduces oxidative markers such as MDA, increases BDNF, and decreases pro-inflammatory cytokines and NF-κβ signalling (L. Zhang *et al*., 2023). Naringenin also restores altered tryptophan and serotonin levels in mice (Gao *et al*., 2022).

Rosmarinic acid

It is a key compound in *Rosmarinus officinalis* that protects the liver and heart, lowers inflammation, combats oxidative stress, and slows aging. Studies suggest it benefits depression by affecting genes governing GABAergic, serotonergic, and dopaminergic pathways (Dahchour, 2022). Both *in vivo* and *in vitro* experiments confirm its antidepressant effects via modulation of cholinergic and monoaminergic systems. Rosmarinic acid alleviates depression in mice by modifying HPA axis activity, MAPK signalling, upregulating BDNF and increasing dopamine (Kondo *et al*., 2015). It may enhance PC12 cell cholinergic activity through ERK1/2 and MAPK pathways, further regulating neurotransmitter systems (Makhathini *et al*., 2018).

Epigallocatechin-3-O-Gallate (EGCG)

It is an abundant in green tea that has anti-inflammatory properties, protects against hippocampal DNA damage and apoptosis, and has anti-depressant effects by reducing neuroinflammation (Platero *et al*., 2021). EGCG balances excessive NO generated during chronic stress, preventing neuronal death and improves memory and behavioural outcomes (B. Lee *et al*., 2018). In animal models, EGCG relieves cognitive impairment and prevents decline in BDNF after stress exposure. This inhibits hippocampal proinflammatory cytokines, and regulates neurosteroid production and HPA axis to reduce stress (Abdelmeguid *et al*., 2022; Y. Zhang *et al*., 2024).

CONCLUSION

Depression remains a pervasive and multifactorial psychiatric disorder with profound personal, societal and economic consequences. Despite advances in pharmacological and psychotherapeutic interventions, current treatments often fall short due to delayed onset, limited efficacy and poor tolerability, particularly in inflammation-associated and treatment-resistant subtypes. The complex pathophysiology of depression-encompassing genetic, epigenetic, neuroendocrine, immune and environmental factors that demands a more integrative therapeutic approach that addresses core neurobiological deficits such as neuroinflammation, oxidative stress, mitochondrial dysfunction and impaired neuroplasticity.

Natural Products (NPs) are derived from diverse botanical, marine, and microbial sources, offer a promising complementary or alternative strategy. Their multi-target mechanisms ranging from modulation of neurotransmitter systems and neurotrophic signaling to anti-inflammatory and antioxidant effects that align closely with the multifaceted nature of depression. Compounds such as apigenin, resveratrol, baicalin, berberine, saffron, curcumin and others have demonstrated antidepressant-like effects in preclinical and emerging clinical studies by enhancing BDNF expression, restoring HPA axis balance and protecting against neurodegeneration.

However, challenges remain in translating these findings into clinical practice. Issues such as poor bioavailability, variability in phytochemical composition, limited long-term safety data and lack of standardized regulatory frameworks hinder widespread adoption. Future research should prioritize well-designed clinical trials, advanced innovative systems (nanoparticle encapsulation and liposomal formulations) and mechanistic studies to validate efficacy and safety. Additionally, investigating research clinical trial designs, multi-omics integration and personalized medicine approaches of NPs may extensively help to manage the depression.

In conclusion, natural products represent a valuable and underexplored reservoir of neuroprotective agents with the potential to fill critical gaps in current depression management. Their integration into therapeutic paradigms could offer more holistic, personalized and sustainable solutions for individuals suffering from this debilitating condition.

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ABBREVIATIONS

5-HT: Serotonin; **ACC:** Anterior Cingulate Cortex; **ACTH:** Adrenocorticotropic Hormone; **AMPK:** Amp-Activated Protein Kinase; **AMPK/mTOR:** Adenosine Monophosphate-Activated Protein Kinase/Mammalian Target of Rapamycin; **BBB:** Blood Brain Barrier; **BDNF:** Brain-Derived Neurotrophic Factor; **BDNF-TrkB-mTOR:** Brain-Derived Neurotrophic Factor, Tropomyosin-related Kinase Receptor B, Mammalian Target of Rapamycin; **DA:** Dopamine; **DAMPs:** Damage-Associated Molecular Patterns; **CaMKII:** Calmodulin-Dependent Protein Kinase II; **CAMKII:** Calcium/Calmodulin-Dependent Protein Kinase II; **cAMP:** Cyclic Adenosine Monophosphate; **CBT:** Cognitive Behavioural Therapy; **CEN:** Central Executive Network; **COVID-19:** Corona Virus Disease 2019; **COX2:** Cyclooxygenase-2; **CREB:** Camp Response Element Binding Protein; **CRH:** Corticotropin Releasing Hormone; **CRHR1:** Corticotropin Releasing Hormone Receptor 1; **CUMS:** Chronic Unpredictable Mild Stress; **CRP:** C-Reactive Protein; **DMN:** Default Mode Network; **DTD:** Difficult-to-Treat Depression; **DALYS:** Disability Adjusted Life Years; **EAAT:** Excitatory Amino Acid Transporters; **EGCG:** Epigallocatechin-3-Gallate; **ELA:** Early life Adversity; **ECT:** Electroconvulsive Therapy; **ECR:** Experiences in Close Relationships; **ETC:** Electron Transport Chain; **ERK:** Extracellular Signal-Regulated Kinase; **FKBP:** FK606 Binding proteins; **FKBP:** FK506-Binding Protein 5; **GABA:** Gamma-Aminobutyric Acid; **GSK3β:** Glycogen Synthase Kinase 3 beta; **HDAC:** Histone Deacetylases; **HPA:** Hypothalamic-Pituitary-Adrenal; **HPA Axis:** Hypothalamic-Pituitary-Adrenal Axis; **IGH:** Insulin like Growth Factor; **IDO:** Indoleamine 2,3-Dioxygenase; **IGH-1:** Insulin-like Growth Factor 1; **IL:** Interleukin; **iNOS:** Inducible Nitric Oxide Synthase; **LPS:** Lipopolysaccharide; **MAPK:** Mitogen Activated Protein; **MAO:** Monoamine Oxidase; **MAOIs:** Monoamine Oxidase Inhibitors; **MBCT:** Mindfulness Based Cognitive Therapy; **MDD:** Major Depressive Disorders; **MFT:** Multifamily Therapy; **mTOR:** Mammalian Target of Rapamycin; **NF-κB:** Nuclear Factor Kappa B; **NLRP3:** NOD-, LRR- and Pyrin Domain-Containing Protein 3; NMDA: N-methyl-D-Aspartate; **nNOS:** Neuronal Nitric Oxide Synthase; **NPs:** Natural Products; **OT:** Oxytocin; **p38 MAPK:** P38 Mitogen-Activated Protein Kinase; **PI3K/Akt:** Phosphoinositide 3-Kinase/Protein Kinase b Pathway; **PSD95:** Postsynaptic Density Protein 95; **Rac1:** Ras-Related c3 Botulinum Toxin Substrate 1; **ROS:** Reactive Oxygen Species; **rTMS:** Repetitive Transcranial Magnetic Stimulation; **SCFAs:** Short Chain Fatty Acids; **SERT:** Serotonin Transporter; **SGK1:** Serum and Glucocorticoid-Induced Kinase 1; **SLC6A4:** Solute Carrier 4A4; **SOD:** Superoxide Dismutase; **SN:** Salience Network; **SSNRIs:** Serotonin-Norepinephrine Reuptake Inhibitors; **SSRIs:** Selective Serotonin Reuptake Inhibitors; **SYP:** Synaptophysin; **TCAs:** Tricyclic Anti-Depressants; **TLR:** Toll-like Receptor; **TNF-α:** Tumor Necrosis Factor-Alpha; **TMS:** Transcranial Magnetic Stimulation; **TRD:** Treatment-Resistant Depression; **TrkB:** Tyrosine Kinase b; **tSYP:** Total Synaptophysin; **VEGF:** Vascular Endothelial Growth Factor.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHOR CONTRIBUTIONS

Manjunatha Pai C: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review and Editing, Visualization.

Rajesh K S: Conceptualization, Validation, Formal analysis, Curation, Writing - Original Draft, Writing - Review and Editing, Visualization.

SUMMARY

Depression is a multifactorial psychiatric disorder with significant global health and economic impact, driven by genetic, neuroendocrine, immune, and environmental factors. Current antidepressants, while effective for some, are limited by delayed onset, incomplete remission rates, and poor tolerability. Natural Products (NPs) from botanical and other sources offer promising multi-target neuroprotective effects-modulating neuroinflammation, oxidative stress, neurotransmitter balance, neuroplasticity, and HPA axis function. Compounds such as apigenin, resveratrol, baicalin, berberine, saffron, curcumin, and others have shown antidepressant-like activity in preclinical and emerging clinical studies. However, their translation into mainstream therapy is hindered by challenges including poor bioavailability, variability in composition, limited long-term safety data, and lack of regulatory standardization. Integrating NPs with modern personalized and multimodal treatment strategies could address unmet clinical needs, but requires robust clinical trials, advanced delivery methods, and mechanistic validation.

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