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Review Article

Plant-Based Antidepressants: An Overview of Bioactive Compounds and Screening Strategies

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Abstract

Depression is a complicated mental illness that affects mood, cognition, and neuroendocrine function. Despite the widespread use of synthetic antidepressants, their limited efficacy, delayed onset of action, and adverse effects underscore the need for safer and more effective substitutes. Therefore, it appears vital to find effective treatments with sufficient efficacy, fewer side effects, and a cheaper cost. Phytoconstituents, such as alkaloids, flavonoids, saponins, terpenoids, and phenolic acids, exhibit antidepressant potential by altering monoaminergic neurotransmission, reestablishing the hypothalamic-pituitary-adrenal (HPA) axis, enhancing brain-derived neurotrophic factor (BDNF) expression, and reducing oxidative stress and inflammation. All of these pathways were found to be involved in the pathophysiology of depression. All things considered, though, plant-based substances provide a promising foundation for the methodical and scientific creation of next-generation antidepressant therapies.

Keywords: Depression; Antidepressants, medicinal plants, herbal medicine, bioactive compounds

INTRODUCTION:

Every year, suicide claims the lives of almost 800,000 people globally. The annual suicide rate in Africa is almost 11 per 100,000, compared to the global average of 9 per 100,000. The American Association of Suicidology (2009) states that depressive episodes are linked to about two-thirds of suicide cases. An estimated 280 million individuals worldwide suffer from depression, making it a serious public health issue. Prevalence rates for women are almost twice as high as for men. Depression, the most prevalent mental disorder, significantly lowers general quality of life, increases the risk of disability worldwide, and has a significant financial burden on both individuals and families.[1] The World Health Organisation (WHO) acknowledges depression as a serious illness and one of the most crippling conditions in the world. According to the global burden of disease, depression is expected to rank as the second most common cause of disability in 2020. Loss of interest, melancholy, reduced appetite, guilt, sleep difficulties, difficulty concentrating, and other mental diseases are all signs of depression. The chronic or recurrent character of certain mental diseases primarily hampers the ability to do daily duties. Approximately 20% of people worldwide suffer from depression.[2] The most common affective disorder is depression, which is defined as a disturbance of mood rather than thought or cognition. It can range from moderate, nearly normal circumstances to severe psychotic depression with delusions and hallucinations. Depression is one of the main causes of disability and early death worldwide. Major depression is still common and significantly increases morbidity and mortality despite advancements in therapy. One in ten people may suffer depression at some point in their lives, and it is linked to almost 70% of the 40,000 suicides that take place in the US each year. Antidepressants are the primary treatment option, with 65–80% of patients seeing some improvement.[3] Approximately 50% of individuals with depression either reduce their antidepressant dosage or quit using psychiatric medications entirely due to severe side effects.

Traditional problems and the high cost of conventional medications have sparked interest in plant-based alternatives. To improve health and wellness, phytotherapy has long been utilised in conjunction with conventional medical techniques like Ayurveda and Traditional Chinese Medicine (TCM). Due to limited access to contemporary allopathic care, rural residents

in many developing nations heavily rely on herbal therapy.[4] More than 80% of medications developed in the 19th century came from botanical sources, demonstrating the historical relevance of plants in the development of medicine. A variety of psychological illnesses can be successfully treated with medicinal plants, which are frequently less expensive and have fewer adverse effects than traditional medications.

For example, natural substances such as α-pinene, α-mangostin, myrsinoic acid, and Mogroside V have been found to be promising candidates for novel antidepressants or as supplements to enhance existing treatments. It is consequently crucial to comprehend how these therapeutic herbs work.[5] Although their frequent side effects may lessen their therapeutic efficacy, synthetic medications are frequently employed as the main treatment for clinical depression. Dry mouth, exhaustion, respiratory and digestive issues, anxiety, agitation, sleepiness, and even heart arrhythmias are typical adverse effects. These medications may also result in a variety of drug-drug interactions. These difficulties emphasise the need for alternate strategies, especially those that make use of medicinal herbs. This study intends to investigate the role of medicinal plants in controlling depression because all of the synthetic antidepressants now available on the market have potential problems and adverse effects.[6]

Psychological problems, including despair and anxiety, with symptoms like melancholy, worthlessness, insomnia, anger, and suicidal thoughts, have been brought on by the COVID-19 pandemic and quarantine. Depression can be categorised as bipolar (familial, frequently beginning in early adulthood) or unipolar (common, associated with life events). Changes in the neurotransmitters norepinephrine, dopamine, and serotonin are the primary cause of this condition, which can be triggered by biological, genetic, or psychological factors. Herbal and natural remedies are a good substitute for pharmaceuticals, which can lead to problems, side effects, and recurrence.[7]

PATHOPHYSIOLOGY OF DEPRESSION:

Depression is a complicated condition that is influenced by biological, psychological, and environmental factors. Its pathophysiology is intimately linked to neurotransmitter abnormalities, such as those involving serotonin, norepinephrine, and dopamine, which affect mood, motivation, and cognition. Reduced neuroplasticity limits the brain's ability to adapt and recover from stress, but inflammatory processes and elevated cytokines can disrupt normal neural activity.[8] Additionally, a genetic predisposition increases susceptibility, especially when combined with stressful life experiences. Moreover, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis can damage mood-regulating brain regions and result in prolonged stress reactions and excessive cortisol release. Together, these components show how complex biological and environmental interactions explain depression.[9]

Neurotransmitter Dysregulation: The monoamine hypothesis, one of the oldest and most prominent theories, suggests that depression is associated with reduced activity or disrupted signalling of key neurotransmitters in the central nervous system, such as serotonin (5-HT), dopamine (DA), and norepinephrine (NE). Anomalies in excitatory (glutamate) and inhibitory (GABA) neurotransmission have also been linked to disruptions in mood, motivation, and cognitive functioning.[10]

Neuroplasticity and Structural Brain Alterations: According to research, depression is linked to reduced neuroplasticity and structural alterations in key brain regions such as the hippocampus, amygdala, and prefrontal cortex. Lower levels of brain-derived neurotrophic factor (BDNF), which weaken synapses and reduce neuronal survival, are primarily responsible for the emotional and cognitive impairments observed in depressive disorders.[11]

Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation: Long-term stress plays a significant role in the development of depression. Hippocampal neurons are destroyed by excessive cortisol release brought on by HPA axis dysfunction, which also disrupts normal neurotransmitter activity. Persistently high cortisol levels, or hypercortisolaemia, are associated with inadequate negative feedback regulation and excessive stress reactivity.[12]

Inflammation and Immune System Involvement: An increasing body of evidence indicates a strong correlation between depressive illnesses and inflammation. Depression symptoms are exacerbated by elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which disrupt neurotransmitter function and impede neurogenesis. The "cytokine hypothesis of depression" is based on these observations.[13]

Genetic and Epigenetic Factors: The heritability of depression is thought to be between 40 and 50 per cent because of genetic predisposition, according to twin and family studies. Additionally, environmental stress alters the expression of genes that regulate stress pathways and neuroplasticity through interactions with epigenetic mechanisms like as DNA methylation and histone modification.[14]

MECHANISTIC INSIGHTS AND THERAPEUTIC POTENTIAL OF HERBAL REMEDIES:

Depression is a common and severe neuropsychiatric condition that manifests as physical symptoms, anhedonia, cognitive impairment, and a consistently low mood. Monoaminergic neurotransmission disorders, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, neuroinflammation, oxidative stress, poor neurogenesis, and decreased brain-derived neurotrophic factor (BDNF) levels are all strongly associated with its pathophysiology.[15]Long-term usage of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) is frequently linked to poor patient compliance, side effects, and delayed onset of action, despite the fact that these medications are

effective classical antidepressants. As a result, herbal treatments that use multi-target pathways with enhanced tolerance to produce antidepressant effects have become more well-liked.[16]

Ashwagandha (*Withania somnifera*): It has long been recognised as a rasayana (rejuvenating herb) that supports healthy ageing, mental clarity, and physical vigour. It is commonly known as Indian ginseng. The medicinal properties of W. somnifera are primarily attributed to a unique class of steroidal lactones known as withanolides, which include withanosides, withaferin A, and withanolide A. Other substances like alkaloids, flavonoids, saponins, and sitoindosides also affect its biological activity. These compounds have anti-inflammatory, immunomodulatory, neuroprotective, and antioxidant qualities.**[17]** The antidepressant effects of W. somnifera are mediated by a number of complementary mechanisms. Ashwagandha has a potent adaptogenic effect that reduces cortisol levels and lessens the neurochemical alterations caused by stress by regulating the hypothalamic-pituitary-adrenal axis. By altering monoaminergic neurotransmission, it improves noradrenergic, dopaminergic, and serotonergic signalling—all crucial pathways in mood regulation. Ashwagandha's increased activation of γ-aminobutyric acid (GABA) receptors is also responsible for its anxiolytic and mood-stabilising effects. Its antioxidant and anti-inflammatory qualities further protect neuronal cells from the oxidative stress and neuroinflammation associated with depression.

Aparajita (*Clitoria ternatea*): *Clitoria ternatea* L., also known as Aparajita or butterfly pea, is a perennial climber that grows throughout tropical Asia, including India. In traditional Ayurvedic and folk medicine, the herb has been used as a Medhya Rasayanam (brain tonic) to enhance mental health, intelligence, and memory. Anxiety, depression, insomnia, and cognitive issues are all treated with the plant's roots, leaves, flowers, and seeds.[18]Its benefits as an additional or alternative therapeutic option in the integrative treatment of depression are highlighted by its neuroprotective, adaptogenic, and neuromodulatory properties. The neuropharmacological action of C. ternate is due to its diverse phytochemical composition. The plant also contains triterpenoids, alkaloids, saponins, phenolic compounds, anthocyanins, especially ternatins, which give the plant its characteristic blue colour, and flavonoids like quercetin, kaempferol, and myricetin. These bioactive components are highly relevant to the pathophysiology of depressive disorders due to their well-known potent antioxidant, anti-inflammatory, and neuroprotective qualities.[19]

Hypericum Species (*H. perforatum* L. and *H. maculatum* C): One of the medicinal herbs that has been studied the most for the treatment of depression is Hypericum perforatum L., also known as St. John's wort. Because of its good efficacy and tolerance profile, it has been used extensively in clinical practice for the treatment of mild to moderate depression. H. perforatum's rich phytochemical composition—which includes naphthodianthrones like hypericin and pseudohypericin, phloroglucinol derivatives like hyperforin, and a wide range of flavonoids including quercetin, rutin, and kaempferol—is responsible for its pharmacological effectiveness.[20] Together, these components suppress the reuptake of monoamine neurotransmitters (serotonin, dopamine, and norepinephrine), alter glutamatergic transmission, control the functioning of the hypothalamic-pituitary-adrenal axis, and have anti-inflammatory and antioxidant properties. All of these processes work together to support its neuroprotective potential and antidepressant effectiveness.[21]

Brahmi (*Bacopa monnieri* Linn): Typically referred to as Brahmi, this plant thrives in the wet, swampy, and marshy areas of India and other subtropical regions. In traditional Ayurvedic medicine, Bacopa monnieri is categorised as a medhya rasayana and has long been used to improve cognitive abilities, memory, and mental clarity, as well as to treat neuropsychiatric conditions like anxiety, depression, and stress-related disorders. Modern pharmacological studies further validate these traditional uses, emphasising. It has promising antidepressant and anxiolytic effects.[22]The rich amount of triterpenoid saponins, or bacosides (bacoside A and bacoside B), which are thought to be the main bioactive markers, is largely responsible for B. monnieri's medicinal effectiveness. The plant also contains phenolic chemicals, sterols, flavonoids, and alkaloids (herpestine, brahmine). These components have neuromodulatory, neuroprotective, and antioxidant properties that are intimately related to the neurobiological processes that underlie depression. Enhancing serotonergic neurotransmission and altering dopaminergic and noradrenergic pathways, which improve synaptic signalling and mood regulation, are two of the many interrelated processes that underlie B. monnieri's antidepressant action.[23] By lowering lipid peroxidation and raising endogenous antioxidant enzymes, B. monnieri also has potent antioxidant properties that shield neuronal cells from oxidative stress-induced damage.[24]

Carrot (*Dacus Carota*): Since *Daucus carota* (DC) has historically been used to treat conditions like diarrhoea, acidity, heartburn, and ulcers, the plant's roots were selected to assess its potential as an antidepressant. It is also well-known for its many therapeutic qualities, which include hepatoprotective, enzyme-protective, antifungal, and antibacterial actions. Fever, gonorrhea, anorexia, dysentery, ulcers, and skin conditions have all been treated with it. Numerous bioactive substances, such as carotenoids (β-carotene, α-carotene, lutein), polyphenols, flavonoids, coumarins, terpenoids, vitamins (particularly vitamin A and vitamin C), and essential oils, are responsible for the pharmacological characteristics of D. carota. Carotenoids and phenolic chemicals, which have strong neuroprotective and antioxidant properties, are especially abundant in seeds and roots.[25]D. carota's antioxidant and neuromodulatory qualities are the main mechanisms underlying its antidepressant-like action. Depression is mostly caused by oxidative stress and neuroinflammation, and carotenoids like β-carotene efficiently scavenge reactive

oxygen species, shielding neuronal cells from oxidative damage.[26]

***Eschscholtzia californica*:** The California poppy is commonly known as Eschscholtzia californica Cham. used historically in herbal therapy to treat mood disorders, anxiety, sleeplessness, and nervous agitation. E. californica is non-narcotic and has drawn attention from scientists because to its sedative, anxiolytic, and antidepressant-like qualities, in contrast to opium poppy (Papaver somniferum). The abundance of isoquinoline alkaloids in E. californica, such as californidine, escholtzine, protopine, allocryptopine, and sanguinarine derivatives, is the main cause of its pharmacological activity. The plant also has phenolic chemicals and flavonoids, which support its neuroprotective and antioxidant properties. These components work together to regulate the activity of the central nervous system.[27]There are several ways in which E. California's neuropsychopharmacology actions are mediated. Because of their affinity for γ-aminobutyric acid (GABA) receptors, isoquinoline alkaloids increase inhibitory neurotransmission and have sedative and anxiolytic effects. It has also been proposed that serotonergic and dopaminergic system modification contributes to mood stability and antidepressant-like effects. Furthermore, neurobiological processes linked to depressive illnesses are lessened by antioxidant and anti-inflammatory effects.[28]

APPROACHES TO ANTIDEPRESSANT SCREENING:

A crucial part of neuropsychopharmacology research and drug development is antidepressant screening, which looks for substances that can reduce depressed symptoms by altering central nervous system pathways. Modern screening techniques incorporate behavioural, biochemical, molecular, and translational models to assess both efficacy and mechanism of action due to the complex and multifaceted nature of depression.[29]

In Vitro Screening Approaches: A quick and affordable method for assessing the potential and mechanistic significance of antidepressants is through in vitro experiments. Plant extracts, fractions, and isolated phytoconstituents can all be screened using these models. Monoamine oxidase (MAO-A and MAO-B) inhibition assays, which measure the capacity to stop neurotransmitter degradation; neurotransmitter reuptake inhibition assays, which target serotonin, dopamine, and norepinephrine transporters; antioxidant and anti-inflammatory assays, which measure the reduction of oxidative stress and pro-inflammatory mediators; and neuroprotection and cytotoxicity assays using neuronal and glial cell lines.[30]

In Vivo Behavioural Assays for Antidepressant Activity: Animal behavioural models continue to be the mainstay of antidepressant screening because they can assess both functional and affective outcomes. The Forced Swim Test (FST) and Tail Suspension Test (TST), two often used models that evaluate behavioral despair, Antidepressant-like activity is thought to be indicated by the chronic mild stress (CMS) model, which reflects anhedonia and stress-induced depression; the learned helplessness model, which mimics loss of motivation and cognitive despair; and the reserpine-induced depression model, which assesses monoamine depletion, decreases immobility time, or restores reward-seeking behavior.[31]

Biochemical and Neurochemical Assessment: Biochemical investigations are frequently used to support behavioural outcomes and to demonstrate mechanistic validity. Monoamine neurotransmitter levels, stress hormones such as cortisol and corticosterone, oxidative stress markers and antioxidant enzyme activity, pro-inflammatory cytokines, and neurotrophic factors such as BDNF are examples of biomarkers that enhance the translational relevance of screening results.[32]

Molecular and Genetic Models: Advanced screening techniques include molecular and genetic methods, such as transgenic and knockout animal models, receptor-binding and signalling-pathway tests, and gene-expression studies of depression-related pathways. These techniques enable more thorough investigation of long-term antidepressant processes and target specificity.[33,34]

Translational and Clinical Screening: Promising candidates identified through preclinical screening advance to early-phase clinical evaluation and translational investigations. Human subjects are used to test standardized formulations for pharmacokinetics, acceptability, safety, and efficacy. Antidepressant results are validated using biological markers and clinical rating scales.

LIMITATIONS AND TRANSLATIONAL BARRIERS IN ANTIDEPRESSANT DEVELOPMENT:

The development of successful antidepressant treatments still faces substantial translational and methodological obstacles despite substantial preclinical and clinical research. Limitations in disease modelling, trial design, biomarker validation, and mechanistic alignment between preclinical results and clinical outcomes contribute to high attrition rates during clinical development.[35,36,37]

Limited Predictive Validity of Preclinical Models: Animal behavioural paradigms like the forced swim test and tail suspension test are used in the majority of antidepressant discoveries. [38] These models measure acute stress coping rather than the intricate, long-term aspects of clinical depression, even if they are susceptible to monoaminergic antidepressants. As a result, substances that show promise in preclinical models frequently do not translate into significant therapeutic benefit.[39]

Overreliance on Monoamine-Based Hypotheses: The variability of depressive disorders is not sufficiently captured by traditional antidepressant screening, which places a strong emphasis on monoaminergic processes.[40] Conventional models do not adequately address the dysregulation of neuroinflammatory pathways, neuroplasticity, mitochondrial function, and

the gut-brain axis associated with depression.[41] A treatment plateau and limited innovation are caused by this mechanistic mismatch.

Poor Translatability of Dosing and Exposure: Dose extrapolation is made more difficult by variations in pharmacokinetics, metabolism, and blood–brain barrier permeability between animal models and humans.[42] Many substances fail later-stage studies because they exhibit antidepressant-like effects in animals at levels that are neither safe nor clinically feasible in people.

Lack of Robust Biomarkers: Drug development and therapy monitoring are hampered by the lack of established, clinically significant biomarkers. Animal behavioural outcomes frequently lack direct human counterparts, and clinical diagnosis remains largely symptom-based. Patient stratification and mechanistic validation are compromised by this gap.[43]

Heterogeneity of Depressive Disorders: There are several subtypes of major depressive illness, each with unique biological foundations, making it a clinically diverse syndrome. The majority of clinical trials treat depression as a single condition, which leads to inconsistent treatment outcomes and weak efficacy indicators.[44]This heterogeneity is rarely taken into consideration by preclinical models.

Methodological Limitations in Clinical Trials: Inadequate objectives, short study durations, and high placebo response rates plague many antidepressant trials. While long-term functional and cognitive results are frequently overlooked, subjective evaluation systems may not be sensitive to mechanical improvement.[45]

Inadequate Integration of Sex Differences: There is ample evidence of sex-specific variations in the prevalence, symptoms, and response to therapy of depression. However, clinical trials may not adequately stratify data by sex, reducing generalizability and translational accuracy, while preclinical research frequently uses male animals.[46]

Challenges Specific to Herbal Antidepressants: Variability in phytochemical composition, the absence of standardised extracts, and the complexity of finding active ingredients are further obstacles for botanical antidepressants. Clinical translation is slowed by regulatory frameworks that differ from those of synthesised medicines, and synergistic effects make mechanistic interpretation more difficult.[47]

CONCLUSION:

Since depression is still a complicated and varied neuropsychiatric condition, new treatment approaches outside of traditional monoaminergic antidepressants must be continuously investigated. Preclinical antidepressant screening, which includes molecular methods, in vitro tests, and in vivo behavioural models, has yielded important information on possible therapeutic candidates, including those made from medicinal plants. The importance of herbal antidepressants in contemporary drug discovery is supported by their unique benefits, including neuroprotective qualities, multi-target mechanisms, and positive safety profiles. The low predictive validity of animal models, poor dose translatability, insufficient biomarker integration, and high clinical trial dropout rates are some of the major translational and methodological issues that still exist. In botanical research, these difficulties are exacerbated by problems with phytochemical diversity, standardisation, and regulatory complexity. Future advancements in antidepressant research will rely on the incorporation of validated biomarkers, mechanism-based screening platforms, and precision medicine techniques that take sex-specific variations and illness heterogeneity into consideration. It is anticipated that developments in systems biology, network pharmacology, and translational modelling will improve preclinical research's predictive capacity and make it easier to produce both synthetic and herbal antidepressant treatments. To close the bench-to-bedside gap and provide safer, more effective treatments for depressive disorders, it is imperative to close current methodological gaps.

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