Role of herbal medicines in the treatment of depression: A comprehensive review

Abdul Samad Mohammed[1]*, Nadeem[2], Mukesh Kumar[4], Baljeet Singh[4], Amit Chawla[5]

*[1]*Research Scholar, Department of Health Informatics, Governors State University, University Park, Illinois, United States of America- 60484*

[2]Research Scholar, Department of Public Health, St. Francis College, Brooklyn, New York, United States of America- 11201

[3]Research Scholar, Department of Pharmacy, Jain College of Pharmacy, Usman Kera, Punjab

[4]Director/Principal, Guru Ram Dass group of colleges, Malout, Punjab

[5]Professor cum Principal, Faculty of Pharmacy, Tantia University, Sri Ganganagar, Rajasthan

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Abstract:

Depression is a common mental health disorder characterized by persistent sadness, reduced interest in daily activities, low energy levels, and impaired functional ability. Although conventional antidepressant drugs such as SSRIs, SNRIs, TCAs, and MAO inhibitors are widely prescribed, they are often associated with limitations including delayed onset of therapeutic action, adverse effects, and incomplete recovery in some patients. These limitations have encouraged growing interest in herbal medicines as safer and potentially more effective alternative treatment options. Medicinal plants such as Withania somnifera (Ashwagandha), Hypericum perforatum (St. John's Wort), Bacopa monnieri (Brahmi), Ocimum sanctum (Tulsi), and Curcuma longa (Turmeric) contain important bioactive phytochemicals including alkaloids, flavonoids, and terpenoids. These compounds help regulate neurotransmitters such as serotonin, dopamine, and norepinephrine, which play a key role in mood regulation. In addition, these phytochemicals exhibit antioxidant, anti-inflammatory, and neuroprotective properties that contribute to improvement in mental health and emotional stability. Herbal antidepressants are generally considered well tolerated, economical, and suitable for long-term therapeutic use. However, appropriate standardization, quality control, and clinical validation are essential to ensure their safety, consistency, and effectiveness. Overall, herbal medicines represent a promising complementary or alternative therapeutic approach for the management of depression.

Keywords:

Depression, Herbal Medicines, Herbal Antidepressants, Medicinal Plants, Phytochemicals, Neurotransmitters, Serotonin, Dopamine, Norepinephrine, GABA, Oxidative Stress, Neuroinflammation, HPA Axis, Conventional Antidepressants, Mental Health.

1. Introduction:

1.1. Overview:

Depression is one of the most common mental health disorders affecting adults and represents a substantial public health challenge. Epidemiological data suggest that nearly 10% of the population aged 18 years and above suffer from a depressive disorder each year. The high prevalence of depression underscores its profound impact on individuals and society, contributing to significant emotional distress, impaired social functioning, reduced work productivity, and increased healthcare costs.

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Fig.1. depression

Although effective treatment strategies are widely available, depression remains frequently underdiagnosed and inadequately treated. This treatment gap arises from multiple factors, including poor awareness of depressive symptoms, social stigma surrounding mental illness, insufficient mental health resources, limited access to specialized care, and failure to recognize the disorder during routine clinical evaluations. Importantly, the persistence of untreated depression is not attributable to a lack of safe and effective therapeutic options, as a wide range of pharmacological agents and non-pharmacological interventions have demonstrated clinical efficacy. Timely diagnosis and appropriate management of depression are crucial in minimizing disease burden, enhancing patient quality of life, and preventing severe outcomes such as long-term disability, substance misuse, and suicide. Therefore, improving mental health literacy, strengthening screening and diagnostic practices, and ensuring equitable access to treatment services remain essential components in addressing the growing impact of depression on public health. [1]

The balance between the risks and benefits of conventional antidepressant therapy in bipolar depression has become an area of growing clinical discussion. This debate was largely prompted by the findings of Wehr and Goodwin, who demonstrated that tricyclic antidepressants may provoke manic or hypomanic switching in individuals with bipolar disorder. Moreover, these drugs were found to potentially worsen the overall course of the illness by increasing the rate of mood episode recurrence, thus contributing to a higher risk of rapid cycling. [2]

1.2. Background history:

This article updates an earlier review that explored the role of the history of depression as a potential risk factor for dementia. Following the publication of the original review, several new investigations have emerged, offering further support for the association between past depressive episodes and an elevated risk of dementia. Collectively, these recent studies reinforce the existing evidence and contribute valuable insights into the biological mechanisms and clinical explanations that have been proposed to account for the link between depression and dementia. [3]

1.3. Classification of depression:

Table 1. Classification of depression

S. No.	Type of Depression	Key Features	Duration / Cause
1	Major Depressive Disorder (MDD)	Persistent sadness, loss of interest (anhedonia), fatigue, sleep disturbance, suicidal thoughts	Symptoms present ≥ 2 weeks
2	Persistent Depressive Disorder (Dysthymia)	Chronic low mood, low self-esteem, low energy, poor concentration	Duration ≥ 2 years
3	Bipolar Depression	Depressive episodes alternating with mania or hypomania	Associated with bipolar disorder
4	Psychotic Depression	Severe depression with hallucinations or delusions	Severe form of MDD
5	Postpartum Depression	Sadness, anxiety, irritability after childbirth, difficulty bonding with baby	Occurs within weeks/months after delivery

6	Seasonal Affective Disorder (SAD)	Depression related to seasonal changes, low energy, increased sleep	Common in winter season
7	Atypical Depression	Mood improves temporarily with positive events, increased appetite, hypersomnia	Variant of major depression
8	Premenstrual Dysphoric Disorder (PMDD)	Mood swings, irritability, anxiety before menstruation	Occurs before menstrual cycle
9	Situational Depression (Adjustment Disorder)	Depression triggered by stressful life events	Related to specific stressor
10	Treatment-Resistant Depression	Symptoms do not improve with standard antidepressant treatment	Failure of ≥2 treatments

Above is claasification of depression [4]

1.4. Epidemiology and prevalence of depression:

Antidepressants are among the most commonly prescribed psychiatric drugs and are also widely used medicines in general clinical practice. During the last three decades, their utilization has increased substantially in high-income countries. In the United States, antidepressant use increased by nearly 400% between 1998 and 2008, whereas in the United Kingdom, antidepressant prescribing rates doubled between 1995 and 2011.

Evaluations of electronic prescribing records from five European countries suggest that antidepressant prescribing is comparatively higher in the UK among adults aged 20–60 years, with especially elevated use observed in female populations. In the United States, the annual prevalence of antidepressant use in 2011 was estimated at 14.4%, which is considerably higher than the reported annual prevalence of depression in 2015 (6.7%) and generalized anxiety disorder (2.7%). Collectively, these observations point to a notable mismatch between antidepressant prescribing patterns and the documented prevalence of associated mental health conditions. [5]

Variations in reported prevalence estimates of depression arise from both true differences between populations and the effects of methodological and measurement-related factors. To limit these sources of variation and allow for more reliable cross-national comparisons, the WHO World Mental Health (WMH) Survey Initiative conducted standardized, community-based epidemiological studies using a common research protocol and the WHO Composite International Diagnostic Interview (CIDI), Version 3.0. Across the 18 countries included in the WMH surveys, the 12-month prevalence of DSM-IV major depressive episodes varied from 2.2% in Japan to 10.4% in Brazil, with a median value of around 5%. In addition, prevalence rates were largely comparable between high-income countries (5.5%) and low- to middle-income countries (5.9%), suggesting similar overall levels of depression across different economic contexts. [6]

1.5. Need for Alternative Therapies:

The popularity of these alternative treatments may partly reflect the limitations of current conventional treatments. Prescribing antidepressant medications is the most common approach for treating depression in both women and men. While a wide range of antidepressant medications and strategies for managing depression have been created, these medications are not always effective and are not equally acceptable to everyone. [7]

Community surveys conducted over the past decade show that more than one-third of Americans use complementary and alternative medicine in a given year. It seems likely that people with psychiatric issues use these therapies more often than others. Fatigue, insomnia, chronic pain, anxiety, and depression are among the most frequently reported reasons for using complementary and alternative treatments in community surveys. [8]

1.5.1. Limitations of Synthetic Antidepressants:

Clinically, doctors treat depression with various types of synthetic medicines, but these come with several limitations. Patients often experience side effects, the medications take time to work, and the response and remission rates are low due to the complex nature of depression. Additionally, doctors usually won't prescribe treatment unless the symptoms are harming a patient's work or family life. Synthetic drugs typically target only one issue. In contrast, many plants have flavonoids that can affect several molecular targets and show antidepressant effects. These compounds influence different brain pathways, including noradrenergic, serotonergic, GABAergic, and dopaminergic systems. They also inhibit monoamine oxidase and tropomyosin receptor kinase B while simultaneously enhancing nerve growth and brain-derived neurotrophic factors. [9]

1.5.2. Adverse Effects and Compliance Issues:

Given the ongoing and repeated nature of major depression for most affected individuals, current treatment guidelines suggest continuing antidepressant treatment for 6 to 9 months after an acute episode. In some cases, long-term or even lifelong treatment may be necessary for patients with recurrent forms of illness. To maintain the effectiveness of a chosen antidepressant in those who respond to treatment, the medication must be taken regularly; following the prescribed drug treatment is extremely important. Despite the existence of treatment guidelines that emphasize the need for ongoing treatment beyond the resolution of acute symptoms, the rates of stopping treatment within the first 3 months can reach up to 68%. This varies depending on the type of antidepressant and the treatment setting. [10]

1.6. Role of Herbal Medicine in Mental Health:

The role of herbal medicine in treating various psychiatric disorders has gained recognition over the past decade. Phytotherapeutic preparations like Hypericum perforatum and Piper methysticum have reliable clinical evidence. In 2007, a systematic review of herbal medicines for a range of psychiatric disorders was conducted due to a lack of thorough reviews at the time. Twenty-seven plant medicines were initially reviewed in 2007 using a basic systematic literature search to find relevant trials of herbal medicines for treating major psychiatric disorders. [11]

Depression is a common mental illness that can have a significant impact on a person's health. Most synthetic antidepressants have serious drawbacks. They often have a narrow range of effectiveness, negative side effects, high costs, and symptoms that tend to come back. Many people are increasingly turning to herbal medicine in hopes of finding multi-target antidepressants that are less toxic. The causes of depression are complex. Research indicates that various mental disorders often share some biological changes. [12]

1.6.1. Concept of herbal medicine:

The methods and guidelines for validating modern medicines must also apply to herbal products, even though these products take a holistic approach to treatment. However, traditional concepts of clinical research design can be challenging to apply when evaluating different systems and practices of traditional medicine. This might be because herbal remedies are individualized therapies. [13]

New thoughts should focus on the idea of therapeutic validation and standardizing herbal medicine to tackle the challenges it faces. This presents a significant issue for both the scientific community and social and political leaders. The belief that a whole or partially purified plant extract has benefits over a single isolated ingredient supports the philosophy of herbal medicine. However, most herbalists agree that pharmaceuticals are more effective in emergencies, such as when a patient has dangerously high blood pressure. They maintain that in the long run, herbs can help patients fight off diseases and offer nutritional and immune support that pharmaceuticals do not provide. [14]

1.6.2. Advantages of Herbal Drugs:

1. Natural Origin and Better Biocompatibility:

Herbal drugs are obtained from natural plant sources, including roots, leaves, bark, seeds, and flowers. Owing to their natural origin, these agents are generally well tolerated by the human body and tend to exhibit greater biocompatibility compared with many synthetic drugs. Moreover, traditional medical systems such as Ayurveda, Unani, and Traditional Chinese Medicine have relied on herbal preparations for centuries, providing strong evidence of their long-standing use and compatibility in humans. [15].

2. Fewer Side Effects:

One of the major advantages of herbal medicines is their tendency to produce fewer adverse effects. When used appropriately, they are generally considered safer than many synthetic drugs, particularly during long-term therapy. This improved safety profile is largely attributed to the presence of multiple plant-derived bioactive constituents that act synergistically and in a more balanced manner, rather than exerting an intense effect on a single biological target, which can increase the risk of toxicity. [16].

3. Cost-Effectiveness and Affordability:

Herbal drugs are often more affordable than modern allopathic medicines, as their raw materials are typically locally available and require relatively simple processing without costly manufacturing technologies. This cost advantage enhances the accessibility of herbal medicines, particularly in developing and low-income countries and in rural regions where modern healthcare facilities and pharmaceutical services are limited. [17].

4. Wide Therapeutic Potential:

Herbal drugs exhibit a wide range of pharmacological activities, including anti-inflammatory, antioxidant, antimicrobial, antidiabetic, hepatoprotective, and neuroprotective effects. Owing to the presence of multiple

bioactive constituents, a single herbal drug is often capable of modulating several disease pathways simultaneously, which may contribute to its therapeutic versatility. [18].

5. Suitability for Chronic Diseases:

Herbal medicines are especially valuable in the management of chronic disorders, including diabetes, arthritis, depression, liver diseases, and cardiovascular conditions. As these illnesses often require long-term treatment, herbal drugs are frequently preferred because of their lower toxicity profile and better patient tolerability, which support sustained therapeutic use. [19].

6. Holistic Approach to Health:

Herbal drugs aim not only to treat specific diseases but also to restore overall physiological balance within the body. Traditional herbal medical systems place strong emphasis on enhancing immune function, supporting digestion, and promoting mental well-being, thereby offering a holistic approach to health maintenance and disease management. [20].

7. Reduced Risk of Drug Resistance:

In contrast to many synthetic drugs that act on a single molecular target, herbal drugs contain multiple bioactive constituents. This multi-target mode of action lowers the likelihood of developing drug resistance, particularly in the context of antimicrobial and antiparasitic therapies. [21].

8. Easy Availability and Cultural Acceptance:

Herbal medicines are widely accepted across diverse cultures and traditional healthcare systems. Many medicinal plants are readily available and can be cultivated locally, which reduces reliance on imported pharmaceutical products. In addition, cultural familiarity with herbal therapies enhances patient trust and improves treatment adherence, contributing to better compliance and acceptance. [22].

Chapter 2: pathophysiology of depression:

The prevailing view of the etiology of depression conceptualizes the disorder as arising from a gene–environment (G×E) interaction, like mechanisms proposed for other multifactorial diseases such as cancer, hypertension, and diabetes. Within this model, considerable attention has been directed toward three principal monoaminergic neurotransmitter systems—serotonin (5-hydroxytryptamine, 5-HT), norepinephrine (NE), and dopamine (DA). Progress in molecular neurobiology alongside advances in functional neuroimaging has provided substantial support for the involvement of these systems in the underlying neurobiology of depression. [23]

2.1. Neurobiology of Depression:

Ongoing investigation into the neurobiological mechanisms underlying depression remains essential, yet advances achieved so far have already begun to shape the development of new pharmacological approaches. Several pharmaceutical manufacturers are currently exploring antagonists of corticotropin-releasing factor (CRF) receptors to assess their potential role as antidepressant agents. Alongside this, increasing attention is being directed toward drugs that selectively act on specific serotonin receptor subtypes, which may provide robust antidepressant effects while minimizing stimulation of serotonin receptors not directly implicated in depressive pathology. [24]

2.1.1. Brain Regions Involved:

Major depressive disorder often relates to stress system problems, as shown by unusual hypothalamus-pituitary-adrenal axis function, with cortisol being a key product. An unusual glucocorticoid response is connected to volume changes in the hippocampus, amygdala, and prefrontal cortex in animal research. These brain areas are rich in glucocorticoid receptors, making them possible targets for the harmful effects of too many glucocorticoids. Nevertheless, the changes in the volumes of the hippocampus, amygdala, and prefrontal regions likely arise from other disease mechanisms too, since abnormal cortisol levels are not consistently observed in MDD.

Several neuroimaging studies of MDD in humans have revealed changes in gray matter volumes in areas involved with the hypothalamus-pituitary-adrenal axis, emotion understanding, and regulation, including the hippocampus, amygdala, striatum, medial prefrontal cortex, and anterior cingulate gyrus (ACC). Most studies report smaller volumes in these areas, though the results are

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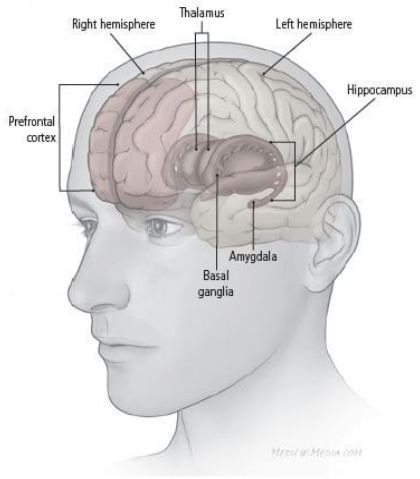

Fig.2. Brain Regions Involved in depression

Not always consistent. Notably, only a few studies have specifically accounted for anxiety comorbidity, despite finding changes in brain structures in anxiety disorders. While volumetric studies in social anxiety disorder (SAD) and generalized anxiety disorder (GAD) are limited, research in panic disorder (PD) has regularly shown altered volumes in the amygdala, insular cortex, dorsomedial prefrontal cortex, and ACC. [25]

2.1.2. Structural and Functional Changes:

limbic-cortical-striatal-pallidal-thalamic circuits (LCSPT), formed by connections between the orbital and medial prefrontal cortex (OMPFC), amygdala, hippocampal subiculum, ventromedial striatum, mediodorsal and midline thalamic nuclei and ventral pallidum (Ongu¨r et al. 2003). The LCSPT circuits initially were related to emotional behavior on the basis of their anatomical connectivity with visceral control structures that mediate emotional expression, such as the hypothalamus and periaqueductal gray (PAG) (Nauta and Domesick 1984). They initially were implicated in the pathophysiology of depression by the observations that degenerative basal ganglia diseases and lesions of the striatum and orbital cortex increased the risk for developing MDE (Folstein et al. 1985). Because these conditions affect synaptic transmission through the LCSPT circuitry in diverse ways, it appears that dysfunction that alters transmission through these circuits in various ways can produce the pathological emotional symptoms encompassed by the MDE criteria. [26]

2.2. Role of Neurotransmitters:

Extensive research has focused on elucidating the links between specific brain neurotransmitter systems and the diverse symptoms of major depressive disorder (MDD). These studies have highlighted that different neurotransmitters play distinct roles in regulating neural activity and behavioral functions. Available antidepressant therapies comprise multiple drug classes that selectively influence these neurotransmitter pathways, while electroconvulsive therapy (ECT) similarly produces therapeutic benefits through modulation of neurotransmitter signaling associated with particular depressive symptoms. As a result, treatment approaches for MDD can be individualized by targeting specific neurotransmitter systems, thereby enabling more effective and symptom-focused clinical management. [27]

2.2.1. Serotonin:

This work examines the emergence of the serotonin hypothesis of depression, the evolution of systematic research in this area, and advances in neurotransmitter imaging technologies, including optogenetic techniques and genetically encoded biosensors. It should be noted that this manuscript is not intended as a systematic review or meta-analysis of serotonergic evidence in depression based on a predetermined theoretical model. Instead, its purpose is to present a historical narrative describing how serotonin came to be linked to depression and how a dedicated research field developed around this neurotransmitter. Although accumulated findings provide strong support for alterations in serotonergic signaling in depression, they also highlight the complex and heterogeneous nature of the disorder. [28]

2.2.2. Dopamine:

Accumulating evidence indicates that reduced dopaminergic neurotransmission plays a significant role in major depressive disorders. The underlying physiological mechanisms responsible for diminished dopamine

(DA) signaling may involve decreased DA release from presynaptic neurons or defects in postsynaptic signal transduction. These defects may stem from changes in dopamine receptor density or functionality and/or alterations in downstream intracellular signaling processes. [29]

2.2.3. Norepinephrine:

Norepinephrine (NE) is an important monoaminergic neurotransmitter with widespread actions across multiple brain regions, where it plays a critical role in regulating arousal and stress-related processes. The cortical noradrenergic system functions to balance vigilance and environmental monitoring with focused attention toward novel or meaningful stimuli, while also influencing overall arousal levels. The central NE system is closely linked to the body's stress-response circuitry, and dysregulation of noradrenergic signaling has been strongly associated with the development of anxiety and depressive disorders. [30]

2.2.4. GABA:

Growing evidence indicates a significant relationship between major depressive disorder (MDD) and disturbances in the GABAergic system. Both clinical and experimental studies suggest that deficits in GABAergic neurotransmission may play an important and possibly causal role in the pathophysiology of depressive disorders. Research involving individuals with depression has demonstrated reduced concentrations of γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter of the central nervous system. Additionally, changes in the subunit composition of GABAA receptors, which mediate inhibitory signaling in the brain, have also been observed. [31]

2.3. Monoamine Hypothesis:

The monoamine hypothesis has historically been one of the most widely accepted explanations for major depressive disorder (MDD) due to its simplicity and clear conceptual basis. This theory proposes that depression arises from deficiencies in key monoamine neurotransmitters within the brain. Accordingly, many currently available antidepressant medications are thought to produce their therapeutic effects by increasing the synaptic availability of these neurotransmitters.

Despite its influence, several limitations of the monoamine hypothesis have been identified. One significant limitation is its inability to account for the delayed onset of therapeutic effects commonly observed with antidepressant drugs. Additionally, a considerable number of patients with MDD show poor or no response to existing antidepressant treatments. These shortcomings have encouraged researchers to investigate alternative or complementary hypotheses, aiming to better understand the mechanisms of antidepressant action and to discover new therapeutic targets for the management of MDD. [32]

2.3.1. Concept of Monoamine Theory:

Depression is among the most common mental health disorders worldwide. It affects people across different age groups and is often associated with substantial impairment in social interactions and daily functioning. In more severe cases, depression may result in suicidal behavior and increased risk of mortality. The overall burden of this disorder has grown significantly in recent years, particularly with the noticeable rise in cases following the COVID-19 pandemic. Several theories have been proposed to explain the pathogenesis of depression, among which the monoamine hypothesis is one of the earliest and most widely recognized. This hypothesis suggests that depressive symptoms arise from alterations in the levels of monoamine neurotransmitters or disturbances in monoaminergic signaling within the brain. Many currently available antidepressant medications are believed to exert their therapeutic effects based on this principle by enhancing monoamine neurotransmission. [33]

2.3.2. Limitations of the Theory:

Antidepressant treatments are closely associated with the monoamine hypothesis, as most currently used antidepressant medications act by influencing the monoaminergic neurotransmitter system. Despite their extensive clinical use, these drugs present several notable limitations. Studies evaluating antidepressant efficacy have shown that around 50% of patients do not respond adequately to the first course of treatment, while approximately 30% remain resistant even after trying multiple therapeutic approaches. In addition, antidepressant medications generally exhibit a delayed onset of action, often requiring several weeks before noticeable clinical improvement occurs. Because the monoamine hypothesis forms the conceptual foundation for many antidepressant therapies, the limited response rates observed in a significant proportion of patients suggest that this hypothesis alone may not fully explain the complex biological mechanisms underlying depressive disorders. [34]

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2.4. Neuroendocrine Factors:

Major depressive disorder is strongly associated with dysregulation of the neuroendocrine system, particularly the hypothalamic–pituitary–adrenal (HPA) axis. In individuals experiencing depression, persistent psychological stress can trigger overactivation of the HPA axis, leading to increased secretion of cortisol from the adrenal glands. Elevated cortisol levels may negatively influence several critical brain regions, including the hippocampus, prefrontal cortex, and amygdala, which are involved in mood regulation, memory formation, and emotional processing. Prolonged exposure to excessive cortisol can disrupt hippocampal neurogenesis and neuronal plasticity, thereby contributing to cognitive impairment and the persistence of depressive symptoms. Beyond HPA axis abnormalities, disturbances in other endocrine systems—such as thyroid hormones and growth hormone regulation—have also been observed in patients with depression. These findings indicate that hormonal imbalance plays a significant role in the pathophysiology of depressive disorders. Furthermore, neuroendocrine dysfunction interacts with genetic predisposition, environmental influences, and psychological stressors, collectively contributing to the onset and progression of depression. [35]

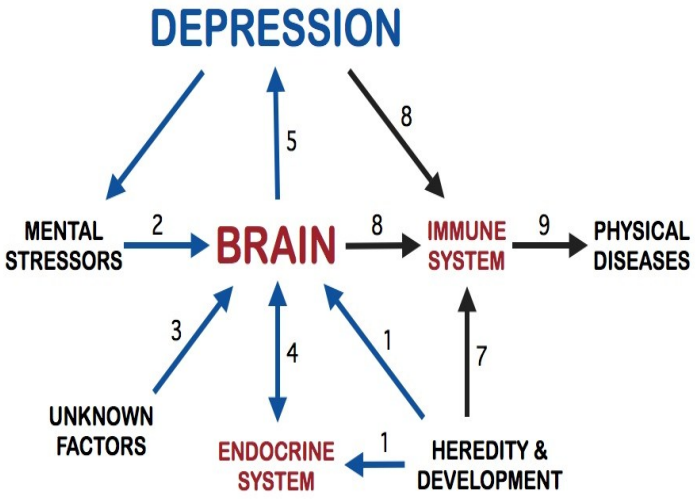

Fig. 3. Neuroendocrine Factors Involved in Depression

2.4.1 HPA Axis:

Stress plays an important role in the pathogenesis of depression, as stressful life experiences may precipitate depressive episodes in individuals with heightened vulnerability. In contrast, adverse experiences during early life—such as childhood abuse or neglect—significantly increase the risk of depression in adulthood. Support for this association is provided by animal studies, which show that exposure to chronic mild stress leads to behavioral alterations in rodents that resemble key depressive symptoms, including reduced pleasure-seeking behavior (anhedonia), lowered motivation, disrupted grooming, and changes in sleep patterns.

From a clinical perspective, depression is commonly linked to abnormal regulation of the hypothalamic–pituitary–adrenal (HPA) axis, indicating an amplified biological response to stress. This dysregulation is characterized by increased release of corticotropin-releasing factor (CRF), impaired negative feedback control, enlargement of the adrenal glands, elevated circulating cortisol concentrations, and diminished cortisol suppression. In certain patients, these abnormalities result in cortisol secretion even in response to low-intensity stressors, along with persistently elevated baseline cortisol levels. [36]

2.4.2 Role of Cortisol:

The role of cortisol in depression is best understood within a broader framework explaining the development of major depressive disorder (MDD). However, establishing such a framework remains difficult due to several conceptual and methodological limitations. One major challenge lies in the uncertain definition of MDD, which continues to rely primarily on clinical symptoms rather than clearly defined biological markers. Furthermore, there are ongoing concerns regarding the validity of psychological constructs used to identify risk patterns, the lack of well-defined physiological characteristics of MDD, and the difficulty of integrating findings from multiple scientific disciplines into a single explanatory model.As a result, synthesizing evidence from psychological, biological, and clinical research into a comprehensive framework that explains the pathways leading to MDD continues to be a complex and evolving task. [37]

2.5. Oxidative Stress and Neuroinflammation:

The importance of cortisol in depression becomes clearer when examined within a broader framework describing the development of major depressive disorder (MDD). However, establishing such a framework remains challenging due to several conceptual and methodological constraints. A major difficulty arises from the uncertain definition of MDD, which still depends largely on clinical symptoms rather than well-established biological markers. In addition, concerns remain regarding the validity of psychological constructs used to describe risk patterns, the absence of clearly defined physiological characteristics of MDD, and the challenge of integrating findings from different scientific disciplines into a unified explanatory model. Consequently, combining evidence from psychological, biological, and clinical research to create a comprehensive model that explains the pathways leading to MDD remains a complex and continuously evolving endeavor. [38]

2.5.1. Role of Free Radicals:

An increase in free radicals could cause this, which would eventually kill cells and cause the atrophy of vulnerable neuronal and glial cell populations in these areas. Consequently, investigations into heightened oxidative stress in unipolar depressive disorder, facilitated by increased levels of free radicals, have been conducted. This review provides a thorough examination of the existing literature regarding the role of oxidative stress and free radicals in depression. [39]

2.5.2 Cytokines and Inflammation:

Recent studies on inflammatory cytokines show that they are a cause of depression. Depression makes cytokines react more strongly to pathogens and stressors. Responses, when coupled with additional predisposing factors, result in extended inflammatory processes, persistent dysregulation of various axes, and manifestations of stress, pain, mood fluctuations, anxiety, and depression. [40]

2.6 Genetic and Environmental Factors:

To investigate the impact of genetic and environmental factors over time, we initiated the longitudinal analyses using a triangular, or Cholesky, decomposition. A Cholesky decomposition is a completely saturated model in which the number of estimated parameters is the same as the number of independent variances and covariances. The number of factors for each latent structure (A, C, and E) is the same as the number of time points. The first factor affects all phenotypes at all five ages. The second factor affects the phenotype at the next age and at all ages after that. The next three factors work the same way, but each one starts one time point later.

The relationships between genetic and environmental factors show how much the same genes or environmental factors affect the stability of the phenotype.

A strong correlation means that the same things are happening, while a weak correlation means that things are changing. The genetic correlations between younger and older ages were minimal, indicating the operation of distinct genes at these stages. The genetic correlations were significantly elevated between the ages of 7 and 12 years, yet they still indicated potential change processes. The correlations among the shared environmental factors were strong, suggesting that these factors were significant during childhood. [41]

2.6.1. Genetic Predisposition:

Genetic predisposition to mental disorders does not guarantee the development of a mental disorder. Nonetheless, possessing a genetic predisposition to disorders diminishes resilience to stressors encountered during puberty, and in the absence of recovery capacity, a mental disorder is precipitated. The significance of epigenetics in preserving normal development and biological functions is evidenced by the fact that the onset of numerous diseases transpires when inappropriate epigenetic marks are introduced, added at inopportune times, or placed in incorrect locations. [42]

2.6.2. Environmental Stressors:

Stress may play a role in the onset and progression of depression as a consequence of various converging factors, including the enduring impact of environmental stressors and the lasting effects of stressful childhood experiences, which may lead to persistent hyperactivity of the hypothalamic-pituitary-adrenal axis. These alterations, encompassing heightened levels of corticotropin-releasing factor and cortisol, are correlated with amygdala hyperactivity, hippocampal hypoactivity, and diminished serotonergic neurotransmission, collectively leading to enhanced susceptibility to stress. [43]

Chapter 3: conventional antidepressant drugs:

Although conventional antidepressants show considerable structural variation, most are classified as monoamine-based drugs, as they primarily enhance the synaptic availability of neurotransmitters such as serotonin, norepinephrine, and dopamine. However, increasing evidence from both preclinical studies and clinical research suggests that agents capable of decreasing neurotransmission at N-methyl-D-aspartate (NMDA) receptors may also exert antidepressant effects. Experimental findings indicate that prolonged administration of antidepressant drugs can influence the gene expression (mRNA levels) of NMDA receptor subunits and alter radioligand binding activity in specific regions of the central nervous system. These observations suggest that both monoaminergic antidepressants and NMDA receptor antagonists may produce therapeutic effects through a common functional outcome, involving a region-specific reduction in NMDA receptor activity, which may contribute to their antidepressant action. [44]

3.1. Classification of antidepressant drugs:

Table 2. Based on the Mechanism of Action

Main Class	Sub-classification	Mechanism of Action	Examples
Monoamine Reuptake Inhibitors	Non-selective monoamine reuptake inhibitors	Inhibit re-uptake of both serotonin and norepinephrine at the synaptic cleft, increasing their concentration in the CNS.	Imipramine (Imizinum), Amitriptyline
	Selective Serotonin Reuptake Inhibitors (SSRIs)	Selectively inhibits serotonin reuptake, thereby enhancing serotonergic transmission, with improved safety and tolerability.	Fluoxetine, Sertraline
	Selective Norepinephrine Reuptake Inhibitors (NRIs)	Inhibit norepinephrine reuptake, increasing adrenergic neurotransmission	Maprotiline
Monoamine Oxidase (MAO) Inhibitors	Non-selective MAO inhibitors (MAO-A & MAO-B)	Inhibits both MAO-A and MAO-B, increasing levels of serotonin, norepinephrine, and dopamine.	Phenelzine, Tranylcypromine, Nialamide
	Selective MAO-A inhibitors	Selectively inhibits MAO-A, increasing serotonin and norepinephrine with a relatively safer profile.	Pirlindole (Pirazidolum), Moclobemide
Atypical Antidepressants	—	Act through mechanisms different from classical antidepressants	Trazodone, Mianserin, Agomelatine, Ademetionine

Table. 3. Based on Additional Pharmacological Action

Class	Pharmacological Effect	Clinical Use	Examples
Thymoleptics	Mood-elevating with a sedative effect	Useful in depression, anxiety, and insomnia	Amitriptyline
Thymoerectics	Mood-elevating with a psychostimulant effect	Useful in depressive states with psychomotor retardation	Nialamidum
Mixed-acting antidepressants	Both sedative and stimulating effects (dose-dependent)	Broad clinical application	Imipramine, Pirlindole

The classification is based on the MOA and the pharmacological action of the drug. [45]

3.1.1. Tricyclic Antidepressants:

Tricyclic antidepressants (TCAs) were first demonstrated to be effective in the prevention of headaches in 1964 and have since become an established therapeutic option for headache prophylaxis. Despite their recognized efficacy, current treatment standards in the United States indicate that approximately 43% of males and 34% of females who are eligible for preventive therapy do not receive appropriate treatment. This treatment gap may be attributed to limited awareness of the magnitude of therapeutic benefits, concerns

regarding potential adverse effects, or the misconception that antidepressant efficacy is restricted primarily to migraine headaches.

Previous meta-analytical evidence has shown that antidepressants are effective in reducing headache frequency in both tension-type headaches and migraine, indicating broader clinical utility. However, earlier analyses were limited by the relatively small number of available studies. To address this limitation, subsequent systematic evaluations have examined the efficacy and tolerability of tricyclic antidepressants in decreasing headache burden among adults suffering from migraine or tension-type headache. [46]

3.1.2. SSRIs:

Selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed medications for the management of depression and anxiety disorders. These agents exert their therapeutic action by inhibiting the serotonin transporter (5-HTT), which results in increased availability of serotonin in the synaptic cleft and enhanced serotonergic neurotransmission. Although SSRIs are generally regarded as safe and are associated with relatively mild adverse effects during long-term use, growing evidence indicates that exposure to these drugs during critical stages of development may have important implications for neurodevelopment.

Research has demonstrated that the serotonin transporter is temporarily expressed in multiple brain regions during early development, where it contributes to neuronal differentiation and the formation of neural circuits. Experimental studies suggest that inhibition of 5-HTT during developmental periods may lead to alterations in neuronal connectivity, particularly in sensory processing systems. Moreover, the behavioral effects associated with 5-HTT inhibition during development appear to differ from those observed when the same mechanism is targeted in adulthood. Much of the supporting evidence has been obtained from studies involving 5-HTT knockout animal models, including mice and rats. Observations in humans also suggest that genetic variations resulting in altered serotonin transporter activity may influence brain development through changes in serotonergic signaling pathways. [47]

3.1.3. SNRIs:

The group of serotonin and norepinephrine reuptake inhibitors (SNRIs) consists mainly of three agents: venlafaxine, milnacipran, and duloxetine. These medications produce their therapeutic effects by inhibiting the reuptake of both serotonin (5-HT) and norepinephrine (NE), thereby enhancing the availability of these neurotransmitters in the synaptic cleft. However, differences exist in their selectivity toward these neurotransmitters. Milnacipran shows approximately equal affinity for inhibiting the reuptake of serotonin and norepinephrine, while duloxetine demonstrates about ten-fold greater selectivity for serotonin, and venlafaxine exhibits nearly thirty-fold greater selectivity for serotonin reuptake inhibition.

All three SNRIs have been shown to be effective in the management of various anxiety disorders, with overall efficacy comparable to that observed with selective serotonin reuptake inhibitors (SSRIs). Nevertheless, in contrast to SSRIs, which generally provide limited benefit in the treatment of chronic pain, SNRIs have demonstrated significant effectiveness in alleviating chronic pain conditions, both in individuals with coexisting depression and in those without depressive symptoms.

The tolerability profile of SNRIs at therapeutic doses varies among individual drugs within this class. Although direct head-to-head comparisons are limited, venlafaxine is often considered less well tolerated due to serotonergic adverse effects, such as nausea, sexual dysfunction, and discontinuation-related symptoms, along with a dose-dependent increase in blood pressure. In contrast, duloxetine and milnacipran are generally better tolerated and are associated with minimal cardiovascular toxicity. [48]

3.1.4. MAO Inhibitors:

Monoamine oxidase inhibitors (MAOIs) are used less frequently in modern psychopharmacological practice, mainly because of concerns regarding possible dietary restrictions and drug interactions. There is widespread misunderstanding about the risks associated with MAOIs, while practical recommendations for their safe and effective use are relatively limited in current literature. Although MAOIs are generally not considered first-line treatment options, they remain valuable therapeutic agents when prescribed carefully by experienced clinicians. In patients with depression, panic disorders, and other anxiety disorders who do not respond adequately to conventional first-line therapies, MAOIs may provide substantial clinical improvement when appropriate monitoring and precautionary measures are followed. [49]

3.2. Mechanism of Action:

A broad range of pharmacological therapies is currently available for the management of major depressive disorder (MDD). The development of many of these medications has not always followed a strictly rational drug design approach; rather, several agents were identified through clinical observations and progressive therapeutic advancements. Tricyclic antidepressants (TCAs) remained the cornerstone of depression treatment

until the 1990s, after which selective serotonin reuptake inhibitors (SSRIs) emerged as the most widely prescribed class of antidepressants due to their improved safety and tolerability profiles. Nevertheless, the relatively poor tolerability associated with TCAs and concerns regarding the therapeutic response to SSRIs in certain patient populations have encouraged ongoing research aimed at identifying more effective treatment alternatives.

As a result, considerable attention has been directed toward drugs that modulate norepinephrine and serotonin neurotransmitter systems, leading to the introduction of several newer antidepressant agents, including venlafaxine, milnacipran, nefazodone, mirtazapine, and reboxetine. Among these, venlafaxine, a member of the serotonin and norepinephrine reuptake inhibitor (SNRI) class, has been associated with a comparatively earlier onset of therapeutic effect and may produce higher remission rates than SSRIs in some patients. These developments highlight the continuing evolution of antidepressant therapy aimed at improving treatment outcomes and patient quality of life.

3.2.1. Reuptake Inhibition:

The mechanism of action of most antidepressant drugs is primarily based on the inhibition of monoamine reuptake transporters, which leads to an increase in the concentration of neurotransmitters such as serotonin, norepinephrine, and dopamine within the synaptic cleft. When an action potential reaches the presynaptic neuron, neurotransmitters are released into the synaptic space, where they bind to specific receptors located on both pre- and postsynaptic membranes, thereby facilitating signal transmission. Under normal physiological conditions, excess neurotransmitter molecules that remain unbound are actively transported back into the presynaptic neuron by specialized transporter proteins containing multiple transmembrane domains. After reuptake, these neurotransmitters are repackaged into synaptic vesicles and stored for release during subsequent neuronal stimulation. This reuptake mechanism plays an important role in regulating neurotransmitter activity and terminating synaptic signaling.

Inhibition of these transporter proteins prevents the reabsorption of neurotransmitters into the presynaptic neuron, resulting in increased neurotransmitter availability in the synaptic cleft and enhanced neurotransmission. This process is considered a fundamental mechanism underlying the therapeutic action of many currently used antidepressant medications. However, this explanation alone does not fully account for the delayed onset of clinical effects often observed during antidepressant therapy. Long-term administration of antidepressant drugs can produce adaptive neurobiological responses that may influence therapeutic outcomes. Persistent inhibition of neurotransmitter reuptake may activate compensatory regulatory mechanisms within the nervous system, including changes in receptor sensitivity and receptor density. Prolonged elevation of monoamine levels in the synaptic cleft may lead to desensitization or downregulation of postsynaptic receptors, particularly serotonin (5-HT) receptors, as part of the body's attempt to restore physiological balance. These adaptive modifications may contribute to differences in patient response and may also explain the occurrence of tachyphylaxis, a condition in which the therapeutic effectiveness of antidepressants gradually decreases despite continued use. [50]

3.2.2. Enzyme Inhibition:

Enzyme inhibition is one of the most commonly utilized approaches in the development of therapeutic drugs. Evaluating the binding affinity of an enzyme inhibitor is an essential step in predicting its biological potency, selectivity, and potential for metabolic interactions in vivo. The inhibition constant (Ki) is widely used as a measure of the strength of interaction between an inhibitor and an enzyme; however, the reliability of Ki as an indicator of in vivo effectiveness largely depends on the accuracy and precision of its determination under in vitro conditions.

Based on this concept, it has been hypothesized that pharmacologically diverse antidepressant drugs and mood stabilizers may exert part of their therapeutic effects through inhibition of monoamine oxidase (MAO). Since MAO enzymes are responsible for the metabolic breakdown of monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine, their inhibition can increase the availability of these neurotransmitters in the brain, thereby contributing to antidepressant activity. [51]

3.3. Limitations of Conventional Therapy:

1. Delayed Onset of Therapeutic Action:

Most conventional antidepressant drugs, including SSRIs, SNRIs, TCAs, and MAO inhibitors, typically require approximately 2–6 weeks before noticeable clinical improvement is observed. This delayed onset of action may prolong patient distress and functional impairment. In severe cases, the waiting period before symptom relief may increase the risk of treatment discontinuation, reduced adherence, or worsening of depressive symptoms, including suicidal ideation.

2. Incomplete Response and Treatment Resistance:

A considerable proportion of patients fail to achieve complete remission with first-line antidepressant therapy. Clinical studies indicate that approximately 30–40% of patients show only partial response or no response at all. Some individuals develop treatment-resistant depression (TRD), which often requires alternative therapeutic strategies such as combination therapy, dose adjustment, augmentation, or non-pharmacological interventions.

3. Adverse Effects and Poor Tolerability:

Conventional antidepressants are frequently associated with a variety of adverse effects that may negatively affect patient comfort and compliance. Common side effects include weight gain, sexual dysfunction, sedation, gastrointestinal disturbances, dry mouth, and constipation, particularly with tricyclic antidepressants. These unwanted effects often reduce patient adherence and may lead to discontinuation of therapy.

4. Risk of Relapse and Recurrence:

Even after successful treatment and symptomatic improvement, many patients experience relapse or recurrence of depressive episodes. As a result, long-term maintenance therapy is often required to prevent recurrence. Prolonged medication use increases the risk of cumulative side effects and may impose an additional psychological and financial burden on patients.

5. Drug Interactions:

Certain classes of antidepressants, particularly monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants, are associated with clinically significant drug and food interactions. For example, MAO inhibitors may interact with tyramine-containing foods, potentially leading to serious complications such as hypertensive crisis. Drug interactions may also increase the risk of serotonin syndrome, a potentially life-threatening condition caused by excessive serotonergic activity.

6. Limited Effectiveness in Certain Types of Depression:

Conventional antidepressant therapies may show reduced effectiveness in specific forms of depression, such as atypical depression, bipolar depression, psychotic depression, or depression associated with chronic medical illnesses. These subtypes often require specialized treatment approaches or adjunctive therapies.

7. Withdrawal and Discontinuation Symptoms:

Abrupt discontinuation of antidepressant therapy may lead to withdrawal symptoms, commonly referred to as antidepressant discontinuation syndrome. These symptoms may include dizziness, insomnia, irritability, headache, anxiety, and flu-like manifestations. Gradual dose tapering is therefore recommended to minimize these effects.

8. Individual Variability in Treatment Response:

Patient response to antidepressant therapy varies considerably due to differences in genetic factors, metabolic activity, disease severity, and coexisting medical conditions. This variability often necessitates a trial-and-error approach to identify the most effective medication and dosage, which may prolong the treatment process. [52]

3.3.1. Side Effects:

Antidepressant medications generally produce comparable therapeutic effects; however, they differ significantly in terms of safety profile and adverse effects. Many of the side effects associated with antidepressants are related to their influence on various neurotransmitter systems, including serotonin, norepinephrine, dopamine, histamine, and acetylcholine. Variations in receptor affinity and pharmacological selectivity contribute to differences in the type and severity of adverse reactions observed among different antidepressant classes.

The occurrence of adverse effects, as well as the inappropriate or irrational use of antidepressant medications, may be partly attributed to limited research in certain areas and insufficient awareness among healthcare professionals regarding optimal prescribing practices and potential drug-related risks. Consequently, inappropriate drug selection or dosing may increase the likelihood of unwanted effects and reduce treatment effectiveness.

Clinical response to antidepressants varies considerably among individuals. Some patients experience significant therapeutic improvement with minimal or mild side effects, whereas others may show only limited benefit or may develop more pronounced adverse reactions. In certain cases, particularly among individuals with mild depressive symptoms, inappropriate or prolonged use of antidepressants may contribute to worsening of symptoms or the development of more persistent depressive conditions. These variations highlight the importance of individualized treatment selection, careful monitoring, and rational prescribing practices to optimize therapeutic outcomes and minimize risks. [53]

3.3.2. Drug Interactions:

Drug interactions are commonly classified into pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic interactions involve alterations in the processes of absorption, distribution, metabolism, or excretion of a drug or its metabolites, which may affect the concentration of the drug within the body. In

contrast, pharmacodynamic interactions occur when two drugs influence the same or related receptor systems, leading to additive, synergistic, or antagonistic effects on physiological function. It is important to recognize that many drug interactions are multifactorial, involving a combination of mechanisms, and may result from a complex sequence of events occurring at both pharmacokinetic and pharmacodynamic levels.

1. Pharmacokinetic Interactions

With few exceptions, most pharmacokinetic interactions involving antidepressant drugs occur primarily at the metabolic level, often involving the hepatic cytochrome P450 (CYP) enzyme system. These enzymes play a crucial role in the oxidative metabolism of many medications and foreign substances, as well as various endogenous compounds such as prostaglandins, fatty acids, and steroid hormones. Alterations in CYP enzyme activity may influence drug concentration in the body, thereby affecting both therapeutic effectiveness and the risk of adverse effects.

2. Pharmacodynamic Interactions

The potential of antidepressant drugs to produce pharmacodynamic interactions varies considerably among different drug classes and largely depends on their mechanism of action and receptor binding profile. Antidepressants that influence a wide range of receptors or enzymatic systems generally possess a greater likelihood of interacting pharmacodynamically with other medications that act on similar biological pathways. This issue is particularly important in elderly patients, who are often prescribed multiple medications simultaneously, thereby increasing the risk of drug interactions. In recent years, however, the overall risk of pharmacodynamic interactions has decreased with the increased use of newer antidepressants, which typically exhibit more selective mechanisms of action and improved safety profiles. [54]

Chapter 4: herbal medicines as antidepressants:

Depression is the most common among the affective disorders, which are characterized primarily by disturbances in mood rather than impairments in thought or cognitive processes. The severity of depression can vary widely, ranging from mild forms that may resemble normal emotional responses to severe psychotic depression, which may be accompanied by hallucinations and delusions. The limitations associated with conventional antidepressant therapies have encouraged the development of new treatment approaches, including the exploration of herbal medicines as potential antidepressant agents. Medicinal plants, particularly those used in traditional Indian systems of medicine, have long been considered an important source of therapeutic compounds for the management of various disorders, including depression. Herbal remedies are often perceived as relatively safe due to their natural origin. In recent years, scientific interest in Ayurvedic herbal medicines has increased, largely because of their historical use and reported effectiveness in treating a wide range of health conditions. Herbal medicine plays a significant role in many traditional healing systems, including Ayurveda, Siddha, Homeopathy, Naturopathy, Traditional Chinese Medicine, and Native American medicine. As a result, considerable research efforts have been directed toward identifying and developing plant-based natural products with potential antidepressant properties. [55]

4.1. Concept of Herbal Antidepressants:

Numerous medicinal plants are traditionally recognized for their potential antidepressant properties and are widely used across different cultures worldwide. It is widely accepted that nature provides valuable therapeutic resources through herbal medicines and natural treatment approaches for the management of various diseases. In the Ayurvedic system of medicine, medicinal plants have been extensively utilized for centuries in the treatment of a wide range of health conditions, including mental disorders such as depression. Consequently, contemporary research has increasingly focused on the scientific investigation and characterization of medicinal plants and their active phytoconstituents, based on traditional knowledge documented in Ayurvedic literature. However, the isolation and extraction of bioactive compounds from plant materials remains a challenging task, as it requires appropriate selection of extraction techniques and analytical methods to ensure reliability, effectiveness, and reproducibility of results. [56]

4.1.1. Definition:

The World Health Organization (WHO) defines herbal medicines as finished, labeled medicinal products that contain active substances obtained from plant sources, including aerial parts, underground parts, or other plant materials, either individually or in combination. Over recent decades, the use of herbal medicines has increased substantially across the world, gaining wide acceptance in both developing and developed nations. This growing interest is largely due to their natural origin, perceived safety, and comparatively lower incidence of side effects when compared with many synthetic medications.

Traditionally, practitioners such as Vaidyas prepared herbal remedies on an individual basis, tailoring treatments according to the specific needs of each patient. In modern times, however, herbal medicines are being produced on a large industrial scale by pharmaceutical companies. This transition from traditional preparation to commercial production has introduced several challenges, including ensuring the availability of good quality raw materials, proper identification and authentication of plant materials, development of suitable reference standards, standardization of formulations, and establishment of appropriate quality control measures.The Ayurvedic system of medicine highlights the long-standing relationship between humans and plants, emphasizing the role of medicinal plants throughout the development of human civilization. Increasing concerns regarding the toxicity and adverse effects associated with certain synthetic drugs have further contributed to the growing demand for herbal therapies, leading to a rapid expansion in the production and use of herbal medicines. Herbal remedies have been an integral part of traditional medical systems since ancient times and continue to be widely used today due to their therapeutic benefits and cultural acceptance in many regions of the world. These natural therapies have made an important contribution to the promotion and maintenance of human health. [57]

4.1.2. Advantages over Synthetic Drugs:

Herbal antidepressants offer several advantages when compared with synthetic antidepressant drugs, mainly because of their natural origin and diverse composition of bioactive compounds. Unlike conventional antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), which usually act through a single pharmacological mechanism, herbal medicines contain multiple phytochemicals, including alkaloids, flavonoids, terpenoids, and phenolic compounds, that produce multi-target effects on the central nervous system. These plant-derived compounds may help in regulating key neurotransmitters such as serotonin, dopamine, and norepinephrine, while also providing antioxidant and neuroprotective benefits. Since depression is a complex disorder involving factors such as oxidative stress, inflammation, and disturbances in neurotransmitter balance, herbal medicines may provide broader therapeutic effects by influencing multiple biological pathways simultaneously. [58]

4.2. Phytochemicals Responsible for Antidepressant Activity:

A variety of chemical constituents found in medicinal plants, as well as in certain fruits and vegetables, have been identified as having potential antidepressant properties. In addition to their therapeutic value, these natural compounds are generally regarded as cost-effective, relatively safe, and useful in the management of multiple health conditions, including cardiovascular diseases, autoimmune disorders, and neurodegenerative illnesses. Many of these biologically active compounds belong to the polyphenol class of phytochemicals, which are recognized for their wide range of pharmacological effects. Notable examples include curcumin, ferulic acid, fisetin, piceatannol, resveratrol, and proanthocyanidins, which have been extensively studied as complementary and alternative therapeutic agents for various diseases, including depression.

These phytochemicals demonstrate multiple biological activities such as antioxidant, anti-inflammatory, antimicrobial, and anticancer effects, which contribute to their protective role in maintaining nervous system health. Their ability to reduce oxidative stress and inflammatory responses, along with their potential influence on neurotransmitter regulation, may contribute to their antidepressant-like activity. As a result, plant-derived polyphenolic compounds have attracted significant attention as promising natural agents for the supportive treatment and management of depressive disorders. [59]

4.2.1. Alkaloids:

Alkaloids are naturally occurring nitrogen-containing organic compounds that are widely present in many medicinal plants. These compounds exhibit significant pharmacological effects on the central nervous system (CNS) and are known to influence key neurotransmitters such as serotonin, dopamine, and norepinephrine, which play an essential role in the regulation of mood, emotions, and behavior. Since depression is often associated with an imbalance in these neurotransmitters, several plant-derived alkaloids have demonstrated considerable antidepressant potential through different mechanisms, including monoamine oxidase (MAO) inhibition, inhibition of neurotransmitter reuptake, neuroprotective effects, and regulation of stress-related pathways.

Some alkaloids exert antidepressant-like effects by enhancing the availability of monoamine neurotransmitters in the brain. For example, harmine, obtained from *Peganum harmala*, acts as a reversible MAO-A inhibitor, thereby reducing the degradation of serotonin and dopamine and increasing their concentration in the synaptic cleft. Berberine, an isoquinoline alkaloid present in *Berberis aristata*, has shown antidepressant activity by modulating serotonergic and dopaminergic pathways, along with providing antioxidant benefits. Reserpine, derived from *Rauwolfia serpentina*, influences the storage of monoamine neurotransmitters within nerve

endings; however, excessive use may lead to depressive symptoms, emphasizing the importance of proper dose regulation.

Furthermore, many alkaloids exhibit neuroprotective and antioxidant properties, which help protect neuronal cells against damage caused by oxidative stress and inflammation, both of which are important factors in the pathophysiology of depression. Due to their strong pharmacological activity even at low concentrations, alkaloids play an important role in the antidepressant potential of several medicinal plants. However, appropriate standardization and controlled dosage are necessary, as alkaloids are biologically active compounds that may produce toxic effects when consumed in excessive amounts.

Examples of Alkaloids with Antidepressant Potential

Harmine	–	Peganum	harmala
Berberine	–	Berberis	aristata
Mitragynine	–	Mitragyna	speciosa
Reserpine	–	Rauwolfia	serpentina

Piperine – Piper nigrum [60]

4.2.2. Flavonoids:

Flavonoids are an important group of plant secondary metabolites that are widely found in medicinal plants, fruits, vegetables, and many dietary sources. These compounds are responsible for providing color, flavor, and aroma to plant-based foods and also contribute significantly to their nutritional and therapeutic value. Flavonoids belong to the larger class of polyphenolic compounds, which are well known for their wide range of biological activities and health-promoting properties. Numerous flavonoids have been reported to possess antioxidant and antidepressant activities, making them valuable natural agents in the management of depressive disorders.

Oxidative stress has been recognized as an important factor in the development of various diseases, including neuropsychiatric disorders such as depression. An imbalance between the production of reactive oxygen species (ROS) and the body's natural antioxidant defense system may result in neuronal damage and impaired brain function. Several studies have demonstrated a close association between oxidative stress and depression, suggesting that compounds with strong antioxidant capacity may help in reducing depressive symptoms. Flavonoids are capable of scavenging free radicals, reducing inflammatory responses, and protecting neuronal cells from oxidative injury, thereby supporting proper neurological function.

Due to these beneficial properties, flavonoids have gained considerable attention as potential natural antidepressant agents. Their combined antioxidants, anti-inflammatory, and neuroprotective effects may contribute to improved mood regulation and overall mental health. Consequently, flavonoid-rich medicinal plants are increasingly being investigated for their potential role in developing safer and more effective therapeutic options for the treatment and management of depressive disorders. [61]

4.2.3. Terpenoids:

Terpenoids constitute an important class of phytochemicals that have been extensively studied for their possible antidepressant activity. These compounds are known to influence several biological mechanisms, including the induction of P-glycoprotein, modulation of hepatic cytochrome enzyme systems, and improvement in the multidrug resistance characteristics of cells. Terpenoids may also alter the plasma concentration of certain drugs, including immunosuppressive agents, through their effects on metabolic pathways. Through these diverse pharmacological actions, terpenoids may contribute to enhanced cellular protection and improved therapeutic outcomes in neurological disorders such as depression.

Depression has been associated with reduced levels of monoamine neurotransmitters, including serotonin, dopamine, and norepinephrine, in the brain. In this regard, saponins, another significant group of plant-derived phytochemicals, have been reported to increase the concentration of these neurotransmitters, thereby supporting normal mood regulation and emotional balance. In addition, hyperactivity or dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, which plays a key role in the physiological response to stress, has been linked to the development of depressive disorders. Certain saponins have demonstrated the ability to normalize HPA axis activity, which may help reduce stress-related hormonal disturbances and contribute to antidepressant effects.

Overall, both terpenoids and saponins exhibit promising therapeutic potential due to their multifunctional pharmacological activities, including regulation of neurotransmitter levels and modulation of stress-response pathways. These properties support their possible role in the development of effective plant-based therapies for the management of depressive disorders. [62]

4.3. Mechanism of Action of Herbal Antidepressants:

Herbal antidepressants produce therapeutic effects through multiple biological mechanisms that help improve mood and alleviate symptoms of depression. Depression is commonly linked with disturbances in neurotransmitter balance, oxidative stress, inflammation, and damage to neuronal cells in the brain. Medicinal plants contain a wide range of bioactive phytochemicals, such as alkaloids, flavonoids, glycosides, terpenoids, and phenolic compounds, which act on the central nervous system (CNS) to restore normal physiological function. These plant-derived constituents demonstrate antidepressant activity and are generally associated with fewer adverse effects compared to many conventional synthetic medications.

4.3.1. Neurotransmitter Modulation:

Herbal antidepressants help regulate important neurotransmitters including serotonin, dopamine, and norepinephrine, which are essential for maintaining mood, sleep patterns, emotional balance, and motivation. Reduced levels of these neurotransmitters are commonly observed in individuals experiencing depression. Many herbal compounds exert their effects by inhibiting monoamine oxidase (MAO) enzymes or by blocking the reuptake of neurotransmitters, thereby increasing their concentration in the synaptic cleft. Enhanced neurotransmitter availability contributes to improvement in mood, reduction in anxiety, and stabilization of emotional responses. [63]

4.3.2. Antioxidant Effects:

Oxidative stress resulting from excessive generation of free radicals can lead to damage of neuronal cells and is considered an important factor in the development of depressive disorders. Herbal medicines are rich in natural antioxidants such as flavonoids, polyphenols, and tannins, which help neutralize free radicals and protect brain tissue from oxidative damage. The antioxidant activity of these phytochemicals helps maintain normal neuronal function, reduce mental fatigue, and support emotional well-being. [64]

4.3.3. Neuroprotective Action:

Many herbal antidepressants also demonstrate neuroprotective properties, which help protect neurons from damage caused by stress, inflammation, and toxic substances. Certain plant-derived compounds promote neuronal survival, enhance synaptic communication, and increase the expression of brain-derived neurotrophic factor (BDNF), an important protein involved in neuronal growth, repair, and plasticity. These neuroprotective effects contribute to improved memory, cognitive function, concentration, and overall mental health. [65]

4.4. Safety and Efficacy of Herbal Drugs:

Herbal medicines used in the treatment of depression are widely considered to be safe and beneficial when taken in suitable doses and prepared using properly standardized formulations. Medicinal plants have been used for many centuries in traditional healing systems such as Ayurveda and Traditional Chinese Medicine for managing depression, anxiety, and stress-related conditions. Modern scientific studies indicate that several herbal antidepressants can produce therapeutic benefits while causing comparatively fewer side effects than many synthetic antidepressant drugs. However, the safety and effectiveness of herbal medicines depend on various factors such as the quality and authenticity of plant material, proper dosage, duration of treatment, preparation method, and the overall health condition of the patient.

4.4.1. Clinical Evidence:

Scientific investigations and clinical observations have supported the antidepressant potential of several medicinal plants. For example, *Hypericum perforatum* (St. John's Wort) has shown positive effects in individuals with mild to moderate depression by improving mood, reducing emotional distress, and helping control anxiety symptoms. Various clinical findings suggest that its effectiveness may be similar to certain conventional antidepressant medicines, but with comparatively better tolerability and fewer unwanted effects. Likewise, *Withania somnifera* (Ashwagandha) has demonstrated beneficial effects in reducing stress, improving mental well-being, and enhancing emotional balance due to its adaptogenic and neuroprotective characteristics. Such findings highlight the growing importance of herbal medicines as supportive therapeutic options in the management of depressive disorders. [66]

4.4.2. Limitations:

Although herbal antidepressants offer several advantages, certain limitations must also be considered. One of the major concerns is the lack of consistent standardization in herbal formulations, which may lead to variation in the amount of active compounds and result in differences in therapeutic response. Some herbal medicines may also interact with conventional pharmaceutical drugs, potentially affecting their effectiveness or increasing the possibility of side effects. Moreover, limited availability of large-scale clinical studies and insufficient scientific validation for certain medicinal plants restrict their wider acceptance in modern medical practice. Therefore, appropriate quality control measures, proper standardization techniques, optimized dosage, and well-designed clinical research are necessary to ensure the safety, reliability, and effectiveness of herbal antidepressant therapies. [67]

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Chapter 5: herbal drugs used in depression:

Depression is a common and serious mental health condition characterized by continuous feelings of sadness, reduced interest or enjoyment in daily activities, low confidence, sleep disturbances, tiredness, and difficulty in maintaining concentration. It affects a large number of people worldwide and has a significant negative impact on overall well-being and quality of life. The development of depression is strongly associated with imbalance of important brain neurotransmitters such as serotonin, dopamine, and norepinephrine, which regulate mood, emotions, and behavior. Various additional factors, including psychological stress, genetic predisposition, hormonal imbalance, and environmental influences, also contribute to the onset and progression of depression. Although synthetic antidepressant medications such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are widely used in clinical practice, these drugs may produce several unwanted effects such as nausea, weight gain, sexual problems, sleep disturbances, and withdrawal symptoms during long-term therapy. [68]

Herbal medicines have been utilized for centuries in traditional healing systems such as Ayurveda, Unani, and Traditional Chinese Medicine for the treatment of mental health disorders including depression, anxiety, and stress. Medicinal plants contain a variety of biologically active compounds such as alkaloids, flavonoids, glycosides, saponins, and terpenoids that exhibit antidepressant activity through multiple mechanisms of action. These plant-derived compounds help maintain normal levels of neurotransmitters, reduce oxidative stress, protect nerve cells from damage, and improve the body's resistance to stress. Because of their natural origin and ability to act on multiple biological targets simultaneously, herbal medicines are generally considered safer and better tolerated, especially when used for long-term management, compared with many synthetic antidepressant drugs. [69]

Recent scientific research and clinical investigations have demonstrated the effectiveness of several medicinal plants such as *Hypericum perforatum* (St. John's Wort), *Withania somnifera* (Ashwagandha), *Bacopa monnieri* (Brahmi), and *Rhodiola rosea* in the management of mild to moderate depression. Herbal antidepressants are increasingly being used as complementary and alternative treatment options because they provide multiple therapeutic benefits including anxiolytic, adaptogenic, antioxidant, and neuroprotective effects. Therefore, herbal medicines represent a promising and comparatively safer approach for the effective management of depressive disorders. However, appropriate standardization, quality control, and clinical evaluation are still required to ensure their safety, effectiveness, and consistent therapeutic outcomes. [70]

5.1. Withania somnifera (Ashwagandha):

Withania somnifera (WS), commonly known as Ashwagandha or Winter Cherry, is an important medicinal plant belonging to the family Solanaceae. It grows widely in dry and subtropical regions of India as well as in countries such as Pakistan, Afghanistan, Sri Lanka, South Africa, Egypt, Morocco, and Jordan. In India, Ashwagandha is cultivated mainly in Madhya Pradesh, Uttar Pradesh, the plains of Punjab, Gujarat, and Rajasthan. The plant is known by several regional names such as Punir (Hindi), Ashvagandha (Bengali), Aksan (Punjabi), Amukkira (Tamil), and Tilli (Marathi). In traditional Indian medicine, Ashwagandha is often referred to as "Indian Ginseng" because of its rejuvenating and vitality-enhancing properties. Different parts of the plant, especially the roots, have been used for centuries in traditional healing practices to manage various health conditions.

Fig. 4. Withania somnifera

Extensive pharmacological studies have demonstrated the wide range of biological activities exhibited by *Withania somnifera*. Research has shown that the plant possesses anti-inflammatory, anticancer, antistress, immunomodulatory, and adaptogenic properties. It also produces beneficial effects on the central nervous system, endocrine functions, and cardiovascular health. Ashwagandha is known to enhance the body's ability

to cope with stress and improve physical and mental endurance. Additionally, the plant exhibits antioxidant activity by reducing lipid peroxidation and increasing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase, which help protect cells from damage caused by free radicals.

The major bioactive constituents of *Withania somnifera*, including withaferin A and sitoindosides, contribute to its antioxidant, anti-inflammatory, neuroprotective, immunomodulatory, and anti-aging effects. Studies also suggest that Ashwagandha may influence neurotransmitter systems such as GABAergic and cholinergic pathways, which are involved in regulating brain function, memory, and emotional stability. Because of these multiple pharmacological actions, *Withania somnifera* has been widely studied for its potential role as an adaptogen, antistress agent, antiepileptic, and protective agent in neurodegenerative and neuropsychiatric disorders. Ongoing scientific research continues to evaluate its chemical composition, therapeutic benefits, and safety profile to support its application in modern medical practice. [71]

5.2 Hypericum perforatum (St. John's Wort):

Hypericum perforatum L., commonly known as St. John's Wort, is a perennial medicinal plant belonging to the family Hypericaceae. It is part of the genus Hypericum, which comprises more than 400 species distributed throughout different regions of the world. The plant is native to Europe, West Asia, North Africa, Madeira, and the Azores, and has been widely naturalized in regions such as North America and Australia. Hypericum perforatum commonly grows in open habitats including grasslands, roadsides, forest margins, and disturbed lands. The plant spreads efficiently through underground stems and prolific seed production, allowing it to thrive in a variety of environmental conditions.

Fig. 5. Hypericum perforatum

In recent decades, the consumption of Hypericum perforatum-based products has increased considerably, making it one of the most widely used medicinal herbs globally. Traditionally, the plant has been utilized for treating several health conditions such as wounds, burns, eczema, and gastrointestinal disorders. Ethnobotanical evidence also supports its historical use in the treatment of infectious diseases. However, contemporary scientific research has primarily focused on its antidepressant potential, which has been supported by multiple pharmacological investigations and clinical studies.

The therapeutic activity of Hypericum perforatum is mainly attributed to the presence of bioactive constituents such as hypericin, hyperforin, flavonoids, and phenolic acids. These phytochemicals are known to influence neurotransmitter systems including serotonin, dopamine, and norepinephrine, which play important roles in regulating mood and emotional balance. In addition to its antidepressant properties, recent studies have also investigated its antimicrobial activity against various bacterial and fungal organisms. Due to its diverse pharmacological effects, Hypericum perforatum continues to be extensively researched as a natural therapeutic agent for the management of depression and other related health conditions. [72]

5.3. Bacopa monnieri (Brahmi):

acopa monnieri (L.) Wettst, commonly known as Brahmi, water hyssop, Bramabhi, or Nirabrahmi, is a small creeping medicinal herb that grows mainly in warm, marshy, and wetland environments. It is widely distributed in the Indian subcontinent, East Asia, Australia, and certain parts of the United States. The plant has small, thick, succulent leaves and delicate white to pale purple flowers. The genus Bacopa contains more than 100 species, many of which are adapted to aquatic or semi-aquatic habitats. Because of its high medicinal value, Bacopa monnieri has been widely used in traditional healthcare systems, especially in Ayurveda.

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Fig. 6. Bacopa monnieri

Brahmi has been utilized for several centuries by Ayurvedic practitioners as an important herb for improving brain function and supporting mental health. Classical Ayurvedic texts such as the Charaka Samhita and Sushruta Samhita describe their positive effects on the central nervous system (CNS). Traditionally, Brahmi is considered a brain tonic that helps enhance memory, concentration, learning capacity, and overall intellectual performance. It has also been commonly used in the management of anxiety, stress, and cognitive disorders. Due to these cognitive-enhancing properties, Brahmi is classified as a nootropic herb, meaning it supports brain function and improves mental performance.

Apart from its beneficial effects on the nervous system, Bacopa monnieri has also been traditionally used for the treatment of inflammatory conditions such as asthma, bronchitis, arthritis, and rheumatism. Scientific studies have demonstrated that the plant exhibits anti-inflammatory, antioxidant, and neuroprotective activities, which contribute to its therapeutic effectiveness. In traditional medicine, Brahmi is also regarded as a cardiotonic, nervine tonic, and mild diuretic. Modern pharmacological research has confirmed its beneficial role in improving memory and cognitive performance, while experimental studies suggest that it may help regulate inflammatory processes in various disease conditions.

Due to its diverse pharmacological properties, including nootropic, anti-inflammatory, antioxidant, and neuroprotective effects, Bacopa monnieri continues to be an important medicinal plant used in Ayurvedic formulations aimed at supporting mental health, improving concentration, and enhancing cognitive ability. Ongoing scientific research is further exploring its active chemical constituents and therapeutic potential in neurological and inflammatory disorders. [73]

5.4. Ocimum sanctum (Tulsi):

Tulsi (Ocimum sanctum / Ocimum tenuiflorum) is an aromatic medicinal plant belonging to the family Lamiaceae, believed to have originated in north-central India and now widely distributed across tropical regions. In Ayurveda, tulsi is highly respected and often referred to as “The Queen of Herbs,” “Mother Medicine of Nature,” and an “elixir of life” because of its diverse health-promoting properties. It has traditionally been used in religious practices as well as herbal medicine to support overall physical, mental, and emotional health.

Fig. 7. Ocimum sanctum (Tulsi)

According to Ayurvedic concepts, tulsi has hot and slightly bitter properties that help balance Kapha and Vata doshas. Regular use of tulsi is believed to improve immunity, promote longevity, and enhance the body’s ability to cope with stress. It is considered a natural adaptogen, meaning it helps maintain physiological balance and

improves resistance against physical, emotional, and environmental stress. Tulsi is also traditionally associated with improved stamina, better cognitive performance, clearer voice quality, and healthy skin.

Tulsi has been widely used for managing various health conditions including anxiety, cough, asthma, fever, indigestion, arthritis, skin diseases, infections, and cardiovascular disorders. Modern scientific studies have supported many of these traditional claims and have shown that tulsi possesses significant antioxidant, anti-inflammatory, antimicrobial, immunomodulatory, and antistress properties. Because of its holistic therapeutic actions, tulsi continues to be an important medicinal herb in Ayurveda and is increasingly studied for its potential role in preventing and managing several modern health disorders. [74]

6. Conclusion:

In conclusion, depression is a complex and multifactorial mental health disorder that has a significant negative impact on the overall quality of life of affected individuals across the world. The present study indicates that although conventional antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase (MAO) inhibitors are widely used in clinical therapy, they are often associated with certain limitations. These limitations include delayed onset of therapeutic effect, various adverse reactions, potential drug interactions, and in some cases incomplete response to treatment. Such drawbacks have encouraged researchers to explore safer, more effective, and better tolerated alternative therapies. Herbal medicines have gained importance as promising options due to their natural origin, ability to act through multiple biological pathways, improved tolerability, and relatively lower incidence of side effects.

Several medicinal plants such as *Withania somnifera*, *Hypericum perforatum*, *Bacopa monnieri*, *Ocimum sanctum*, and *Curcuma longa* contain diverse bioactive phytochemicals including alkaloids, flavonoids, terpenoids, glycosides, and phenolic compounds. These phytoconstituents help regulate important neurotransmitters such as serotonin, dopamine, and norepinephrine, reduce oxidative stress, and provide neuroprotective effects. Through these mechanisms, herbal medicines contribute to improvement in mood, reduction in anxiety and stress, and maintenance of emotional balance. In addition, herbal therapies provide advantages such as cost-effectiveness, cultural acceptance, and suitability for long-term administration, especially in chronic disorders like depression. However, certain limitations such as lack of proper standardization, variation in phytochemical composition, insufficient large-scale clinical trials, and the possibility of herb–drug interactions must be carefully considered to ensure safety and therapeutic reliability. Therefore, further scientific investigation, strict quality control measures, and well-designed clinical studies are necessary to establish the effectiveness, safety, and consistency of herbal antidepressants. Overall, herbal medicines represent an important complementary or alternative therapeutic approach in the management of depression and offer considerable potential for developing safe, effective, and holistic treatment strategies for mental health disorders in the future.

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