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Natural Products for the Treatment of Depression: A Review of Signaling Pathways

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ABSTRACT:
Depression is a common mental health condition characterized by persistent feelings of sadness, hopelessness, and a loss of interest in activities one usually enjoys. it can affect anyone, regardless of age, gender, or background. symptoms may include changes in appetite, sleep patterns, and mood, as well as feelings of guilt, worthlessness, and helplessness. depression can be treated with a combination of therapy, medication, lifestyle changes and some herbal treatments. Herbal remedies have been used to treat various health conditions, including depression. While these treatments can be beneficial, it's essential to consult with a healthcare provider before starting any herbal supplements, as they can interact with medications or have side effects. Some of the researches have proved that medicinal plants also have curative property due to the presence of various chemical substances present in plants. Psychological treatments are the first treatments for depression. While treating they can be combined with antidepressant medications in moderate and severe depression. Antidepressant medications include selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine. Antidepressants should not be used for treating depression in children and are not the first line of treatment in adolescents, among whom they should be used with extra caution. The present review is about some of the medicinal plants which possess for the treatment of depression.

Keywords: Depression, immobility, sadness, herbal treatment, serotonin, antidepression.

I. INTRODUCTION

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest. A serious mood disorder, depression is characterized by anhedonia, the reduced ability to experience pleasure, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, difficulty concentrating, and repetitive thoughts of suicide or death. Depression and anxiety are especially common in cancer patients and negatively impact quality of life. One in three patients (32%) experience anxiety, depression, or adjustment disorder, which is characterized by feelings of stress in response to a major event such as a cancer diagnosis. Breast cancer patients were reported to be most affected (42%), followed by those with head and neck cancer (41%) and melanoma (39%).

Conventional management of depression and anxiety disorders is based on pharmacotherapy and psychotherapy. However, antidepressants and anxiolytics act by modulating neurotransmitters that play a crucial role in both central and peripheral nervous system function.

Depression can affect people of all ages, races, ethnicities, and genders. Women are diagnosed with depression more often than men, but men can also be depressed. Because men may be less likely to recognize, talk about, and seek help for their feelings or emotional problems, they are at greater risk of their depression symptoms being undiagnosed or undertreated [1].

There are different types of depression, some of which develop due to specific circumstances. **Major depression** includes symptoms of depressed mood or loss of interest, most of the time for at least 2 weeks, that interfere with daily activities.

- **Persistent depressive disorder** (also called dysthymia or dysthymic disorder) consists of less severe symptoms of depression that last much longer, usually for at least 2 years.
- **Perinatal depression** is depression that occurs during pregnancy or after childbirth. Depression that begins during pregnancy is prenatal depression, and depression that begins after the baby is born is postpartum depression.
- **Seasonal affective disorder** is depression that comes and goes with the seasons, with symptoms typically starting in the late fall or early winter and going away during the spring and summer.

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- **Depression with symptoms of psychosis** is a severe form of depression in which a person experiences psychosis symptoms, such as delusions (disturbing, false fixed beliefs) or hallucinations [2].

ETIOLOGY

The etiology of depression is multifaceted and involves a combination of genetic, biological, environmental, and psychological factors. They are:

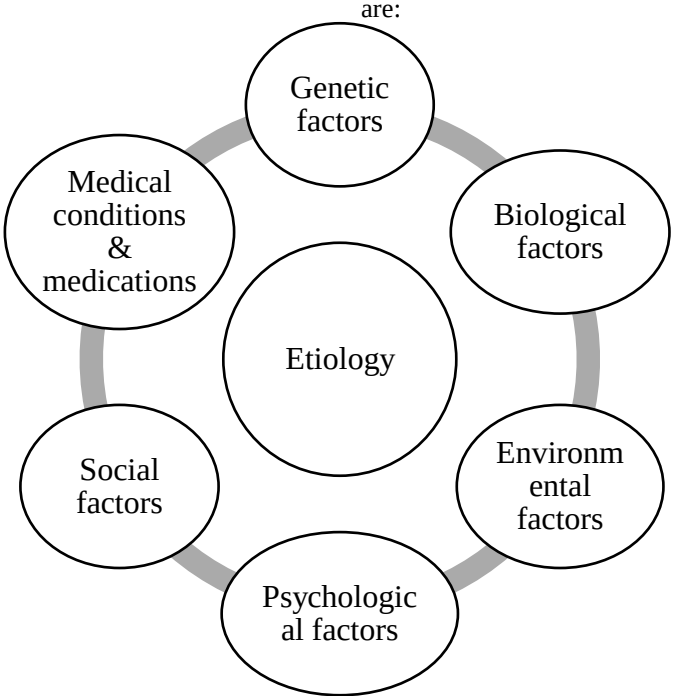

Figure 1: Etiology of depression

Genetic Factors

- **Family Studies**: Research shows that first-degree relatives of individuals with depression are more likely to develop the disorder themselves, suggesting a hereditary component.
- **Twin Studies**: Studies involving identical twins (who share 100% of their genes) show higher concordance rates for depression compared to fraternal twins (who share 50% of their genes) [3].
- **Genetic Research**: Genome-wide association studies (GWAS) have identified multiple genetic loci that may contribute to depression, though each individual gene's effect is small.

Biological Factors

Neurotransmitters:

- **Serotonin**: Often called the "feel-good" neurotransmitter, serotonin is involved in mood regulation. Low levels are commonly associated with depression.
- **Norepinephrine**: This neurotransmitter is involved in the body's stress response. Imbalances can affect energy levels and mood.
- **Dopamine**: Linked to pleasure and reward mechanisms in the brain, disruptions in dopamine levels can influence motivation and enjoyment [4].

Brain Structures:

- **Hippocampus**: Involved in memory and emotion. Depression is associated with reduced hippocampal volume.
- **Prefrontal Cortex**: Plays a role in decision making and regulation of emotions. Depressed individuals may have reduced activity in this area.

Endocrine System:

- **Hypothalamic-Pituitary-Adrenal (HPA) Axis**: Chronic stress can lead to dysregulation of the HPA axis, resulting in elevated cortisol levels (the stress hormone), which has been linked to depression.
- **Thyroid Function**: Hypothyroidism (underactive thyroid) can mimic or contribute to depressive symptoms.

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Environmental Factors

- **Childhood Trauma**: Early adverse experiences, such as abuse, neglect, or loss of a parent, can increase vulnerability to depression later in life.
- **Chronic Stress**: Long-term stress from sources like work, financial difficulties, or caregiving can deplete coping resources and lead to depression.
- **Life Events**: Significant changes or losses, such as divorce, unemployment, or bereavement, can trigger depressive episodes.

Psychological Factors
Cognitive Theories:

- **Beck's Cognitive Triad**: Depressed individuals often have negative views about themselves, their experiences, and their future.
- **Learned Helplessness**: Proposed by Seligman, this theory suggests that exposure to uncontrollable stressors can lead individuals to feel helpless and hopeless, contributing to depression.

Personality Factors: Traits such as neuroticism (tendency to experience negative emotions) can increase the risk of developing depression [5].

Social Factors

- **Isolation and Loneliness**: Lack of social support and meaningful relationships can exacerbate feelings of depression.
- **Cultural and Social Influences**: Stigma, discrimination, and social pressures can contribute to mental health issues.

Medical Conditions and Medications

- **Chronic Illnesses**: Conditions such as cardiovascular disease, diabetes, and chronic pain can lead to depression due to the stress and limitations they impose.
- **Medications**: Certain medications, including some used to treat high blood pressure, chronic pain, and other conditions, can have side effects that include depressive symptoms.

PATHOPHYSIOLIGY

The onset of depression is influenced by a number of factors. Recent research on the pathophysiology of depression has been focused on abnormalities of the monoamine neurotransmitter system, reductions in monoamine synthesis, or dysfunction of the secondary messenger system. Dopamine, noradrenaline, and serotonin (5-HT) are examples of monoamine neurotransmitters that are major mediators of depressed behaviors. These neurotransmitters' diminished function is what leads to depression. One measure of a person's susceptibility to mental illnesses is their level of monoamine oxidase-A (MAO-A) activity. One of the important enzymes involved in the metabolism of neurotransmitters is this one. Moreover, depressive patients have compromised hypothalamic-pituitary-adrenal (HPA) axis function. Corticotropin-releasing factor controls the HPA axis (CRF). When it comes to modulating behavioral, neuroendocrine, and autonomic reactions to environmental stimuli, this physiological regulator is crucial. Depression is indicated by elevated CRF and hyperactivity of the HPA axis. Patients with depression also have higher levels of cortisol, adrenocorticotropic hormone (ACTH), and CRF. Major depressive disorder and adenylyl cyclase activity are related as well. Through the production of cAMP, adenylyl cyclase controls the physiological effects of hormones and medications. Adenylyl cyclase activity is regulated by receptors that are serotonergic. It has been noted in clinical investigations that individuals with depression had less activity of this enzyme than individuals without depression. Oxidative stress is one of the additional variables in the pathophysiology of depression. Tumor necrosis factor-alpha (TNFα) and interleukin 1 beta (IL-1β) are two examples of inflammatory mediators that have been linked to the development of depression in both human and animal models.

In the mammalian brain, glutamic acid and gamma-aminobutyric acid (GABA) function as excitatory and inhibitory neurotransmitters, respectively, and are crucial mediators of anxiety and depression symptoms. As a result, depression is also linked to modifications in these neurotransmitters. Furthermore, glutamate transmission inhibitors have the potential to be antidepressants [6].

Neurobiological Pathogenesis of Depressive Disorder
Glutamate Signaling Pathway

Glutamate is the main excitatory neurotransmitter released by synapses in the brain; it is involved in synaptic plasticity, cognitive processes, and reward and emotional processes. Stress can induce presynaptic glutamate secretion by neurons and glutamate strongly binds to ionotropic glutamate receptors (iGluRs) including

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N-methyl-D-aspartate receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPARs). on the postsynaptic membrane to activate downstream signal pathways. Accumulating evidence has suggested that the glutamate system is associated with the incidence of depression.

Blocking the function of NMDARs has an antidepressant effect and protects hippocampal neurons from morphological abnormalities induced by stress, while antidepressants reduce glutamate secretion and NMDARs [7].

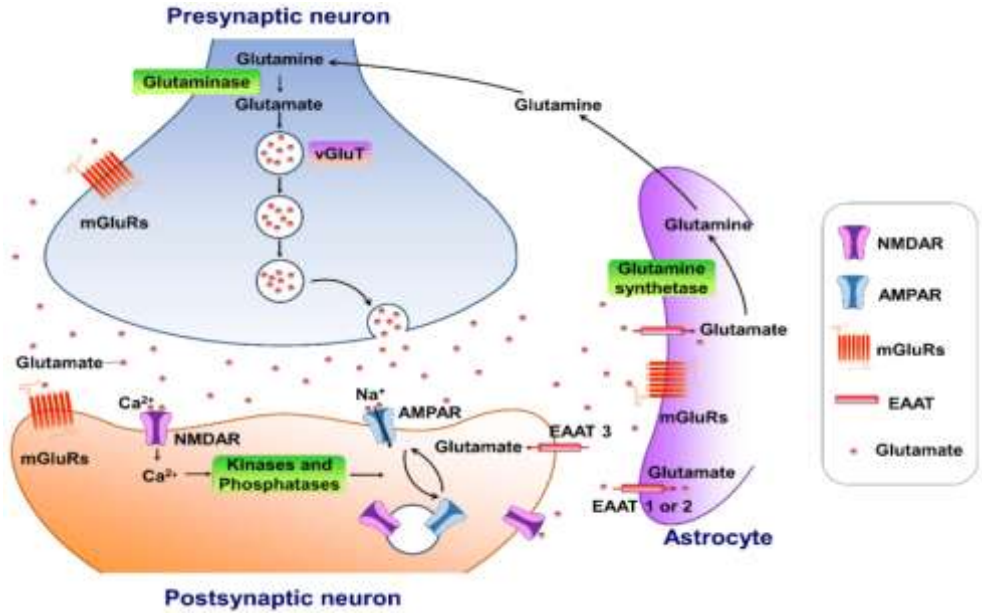

Figure 2: Glutamate Signaling Pathway

Stress-Responsive HPA Axis

Stress is causative or a contributing factor to depression. Particularly, long-term or chronic stress can lead to dysfunction of the HPA axis and promote the secretion of hormones, including cortisol, adrenocorticotropic hormone, corticotropin-releasing hormone, arginine vasopressin, and vasopressin. About 40%–60% of patients with depression display a disturbed HPA axis, including hypercortisolemia, decreased rhythmicity, and elevated cortisol levels. Mounting evidence has shown that stress-induced abnormality of the HPA axis is associated with depression and cognitive impairment, which is due to the increased secretion of cortisol and the insufficient inhibition of glucocorticoid receptor regulatory feedback.

Monoamines

The early hypothesis of monoamines in the pathophysiology of depression has been accepted by the scientific community. This theory of depression is supported by data showing that tricyclic antidepressants and monoamine oxidase inhibitors enhance monoamine neurotransmission. Currently, the first-line antidepressants are still selective serotonin reuptake inhibitors and norepinephrine reuptake inhibitors. Though as many as 15%–40% of depressive patients do not react to many pharmaceutical medications, there are still 1/3 to 2/3 of patients who do not respond well to first antidepressant treatment. As a result, the basic pathophysiology of depression goes well beyond the straightforward monoamine process.

Due to biomarkers for depression and the effects of pharmaceutical treatments, other theories regarding depression have gradually gained more attention. These theories include the neurotrophic family of growth factors, neuro inflammation, neuroendocrine systems, and the stress-responsive hypothalamic pituitary adrenal (HPA) axis [8].

Neuroinflammation

Neurotransmitters are involved in the pathogenesis and pathophysiological processes of depression. Early evidence found that patients with autoimmune or infectious diseases are more likely to develop depression than the general population. In addition, individuals without depression may display depressive symptoms after treatment with cytokines or cytokine inducers, while antidepressants relieve these symptoms. Cytokines

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and chemokines in the circulation activate the central nervous system by regulating the surface receptors of astrocytes and endothelial cells at the BBB. As an intermediary pathway, the immune inflammatory response transmits peripheral danger signals to the center, amplifies the signals, and shows the external phenotype of depressive behavior associated with stress/trauma/infection. Cytokines and chemokines may act directly on neurons, change their plasticity and promote depression-like behavior. Patients with depression show the core feature of the immune-inflammatory response, that is, increased concentrations of pro-inflammatory cytokines and their receptors, chemokines, and soluble adhesion molecules in peripheral blood and cerebrospinal fluid. In addition, a recent study showed that microglia contribute to neuronal plasticity and neuroimmune interaction that are involved in the pathophysiology of depression [9].

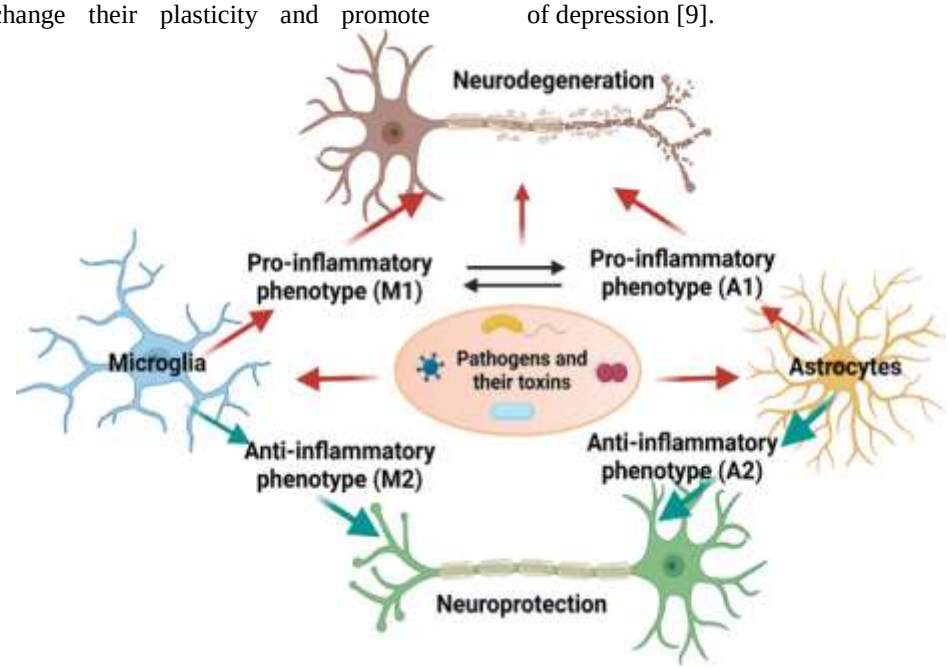

Figure 3: Neuro degeneration

Other Systems and Pathways

There is no doubt that several other systems or pathways are also involved in the pathophysiology of depression, such as oxidant-antioxidant imbalance, mitochondrial dysfunction, and circadian rhythm-related genes, especially their critical interactions (e.g. interaction between the HPA and mitochondrial metabolism, and the reciprocal interaction between oxidative stress and inflammation. The pathogenesis of depression is complex and all the hypotheses should be integrated to consider the many interactions between various systems and pathways.

HERBAL TREATMENT

Herbal medicines exert an effective antidepressant effect, especially in patients with mild-to-moderate depression. In addition, herbal medicines have fewer side effects compared to synthetic antidepressants. Desirable health effects of herbal drugs are largely due to their antioxidant properties and potential impact on cellular metabolism. In recent decades, herbal medicines have been prescribed worldwide as complementary and alternative medicines to treat depression. Medicinal plants can regulate neurotransmission by directly affecting receptors or the synthesis and distribution of neurotransmitters, or by regulating immunological processes. Medicinal plants and their active ingredients also produce therapeutic effects via interaction with serotonergic systems (5-HT3, 5HT2A, 5-HT1A), Noradrenergic (α1 and α2 receptors) and dopaminergic (D1 and D2) receptors. Medicinal plants also regulate the activity of the HPA axis and reduce CRF, and adrenocorticotropin and corticosterone. Some plants remove the symptoms of depression by reducing oxidative stress and inflammatory mediators. The present section addresses the overall antidepressant activity of plants. Plant-derived antidepressant phytochemicals are known to reduce the risk of certain severed is orders, including autoimmune and cardiovascular diseases, as well as neurodegenerative diseases. Some herbal

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drugs have been approved by regulatory authorities for treating psychiatric disorders [10].

Herbal Medicine as Antidepressants

Hypericum perforatum L.

Hypericum perforatum L., is a widely studied medicinal plant that is used to treat depressive symptoms; some of its important chemical components have been shown to exert antidepressant effects. The two main components, hypericin and hyperforin, together with polyphenols and flavonoids, are responsible for these antidepressant effects.

Figure 4: Hypericum perforatum L.

Rhodiola rosea L.

Rhodiola rosea L. (RL), also called "golden root," is used as an herbal plant in northern Europe and some countries in Asia, mainly to improve the symptoms of depression. RL extract elicited depression-like behaviors, such as a decreased sugar preference rate and exploration behavior in mice exposed to CUMS [11].

Figure 5: Rhodiola rosea L.

Lavandula angustifolia Mill. (Lavender)

Combination of imipramine and Lavandula tincture exerted a synergistic effect and was more effective than imipramine treatment alone. Moreover, lavender tincture can be used as a complementary medication in the treatment of mild-to-moderate depression.

Figure 6: Lavandula angustifolia Mill.

Epimedium brevicornum

Suppressing monoamine oxidase, A (MAO-A) and monoamine oxidase B (MAO-B) enzymes and reducing serum malondial- dehyde (MDA) levels.

Figure 7: Epimedium brevicornum

Chrysactiniamexicana

NMDA receptor antagonist and protecting neurons against exci-totoxic effects of NMDA; Increasing the division of stem cells or neuronal precursors in vivo and in vitro, Binding to the benzodiazepine binding site of GABA-A recep-tors and inducing pharmacological properties.

Figure 8: Chrysactiniamexicana

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Chamaemelum nobile
Apigenin present in the plant acts as a ligand of the benzodi-azepine receptor Quercetin inhibits monoamine oxidase.

Figure 9:Chamaemelum nobile

Magnolia grandiflora
Producing effect on the seroton- ergic system; Regulating 5-HT, 5-HIAA, corticosterone and adenylyl cyclase [12].

Figure 10: Magnolia grandiflora

II. CONCLUSION

This conclusion highlights the complexity of depression, causes of depression, underlying mechanisms of depression for neuron damage and the potential role of herbal plants to treat the depression.

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