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Major Depressive Disorder: Pathophysiology and Clinical Management

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Abstract

Depression is a chronic mental disorder that causes changes in mood, thoughts, behavior and physical health. According to the World Health Organization (WHO) 350 people worldwide are said to suffer from this mental disorder. The lifetime prevalence for major depression is reported to be as high as 14-17% and the one-year prevalence is 4-8%. The lifetime prevalence rates of major depressive disorders among women are 10-25%, and for men 5-12%. There are various forms of depression that range from mild to extremely severe conditions like psychotic depression in which the patients show symptoms such as hallucinations and delusions. There are diverse theories on the pathogenesis of depression most based on measurement of indirect markers, post-mortem studies and neuro-imaging techniques. Furthermore, an array of treatment options has been developed to combat depression over the decades. The various approaches include pharmacotherapy, psychotherapy and somatic therapy often employed for treatment resistant depression. Medicinal plants around the world have been used to treat disorders of the body and the mind since antiquity. Herbal medicine has also been a reasonable alternative for the management of mental disorders such as anxiety, depression and dementia among plenty others. Medicinal plants most widely used to treatment depression around the world are *Hypericum perforatum, Centella asiatica*, *Rhodiola rosea*, *Pfaffia paniculata*, *Rauwolfia serpentina*, *Rhododendron molle*, *Schizandra chin*, *Thea sinensis*, *Uncaria tome*, *Valeriana officinalis* and *Withania somnifera.*

Keywords: Major depressive disorders; Herbal antidepressants; Epidemiology; Somatic therapy; Neurotransmitters

Introduction

Overview of depression

Depression is a chronic mental disorder that causes changes in mood, thoughts, behavior and physical health. It's a common but serious disease that can take away a person's ability to enjoy life and cause decline in capacity to undertake even the simplest daily tasks. Other than its chronic nature, symptoms associated with this mental disorder are often recurring and life threatening. According to the World Health Organization (WHO) unipolar depression is one of the leading causes of disability- adjusted life year (DALY) and approximately 350 people worldwide are said to suffer from this mental disorder [1,2].

As described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM- V) [3], the hallmark of major depressive disorder (MDD) is the occurrence of depressed mood (dysphoria) and loss of interest in activities that were rather pleasurable in the past (anhedonia) for a duration of at least two weeks. These symptoms must also be accompanied by at least four of the following manifestations such as changes in appetite or weight, sleep patterns, altered psychomotor activity, feelings of worthlessness or guilt, difficulty concentrating or making decisions and recurrent thoughts of death or suicidal ideation.

Even though there are plenty of drugs developed for the management of depression, one of the challenges in dealing with this disease is that a significant portion of the patients taking antidepressants fail to attain full remission. Some patients also develop treatment resistant depression in which the patients fail to respond to the available drugs or other therapeutic approaches [4].

Types of depression

Depression is a heterogeneous disorder often mistaken for a single clinical mental illness. There are indeed diverse forms of depression that can either be mild or extremely severe conditions like psychotic depression in which the patients show symptoms such as hallucinations and delusions. Diagnosis of this disorder is complicated because of the co-occurrence of many other mental conditions such as anxiety disorders, including panic agoraphobia syndrome, severe phobias, generalized anxiety disorder, social anxiety disorder, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD). This co-morbidity is commonly seen in elderly patients and is also associated with severity of somatic symptoms. [5]. The different types of depression are reviewed below.

• **MDD:** Patients with this type of depressive disorder typically show dysphoric mood and anhedonia accompanied by physical changes such as weight loss or gain, increased or decreased appetite, alteration in sleep pattern and sustained fatigue. Disturbances in cognitive and executive functions are also manifested by lack of concentration and coherent thinking as well as morbid preoccupation by thoughts of death and suicide. Majority of these symptoms normally are present nearly every day and result in significant distress and impaired social life and occupational performance (DSM-V) [3,6].

• **Dysthymic disorder:** It is also known as persistent depressive disorder. Patients display depressed mood or sadness that persists for the majority of the duration of the day for a minimum of two years in adults and one year in children and adolescents. Majority of the patients do not meet the full criteria for MDD as there is interruption by short periods of remission. However, there are instances where patients meet full criteria in which they are diagnosed with MDD [7,8].

• **Melancholic depression:** There is an almost absolute lack of ability

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to experience pleasure. Psychomotor retardation and early morning worsening of mood is also apparent in this subset of patients. This type of depression is seen more commonly in the elderly, in patients with more severe forms of depression and psychotic depression [7].

• **Seasonal affective disorder (SAD):** It is a type of depression described as recurring annually during fall or early winter. This 'winter blues' or SAD is characterized by low mood, feelings of guilt and worthlessness and increased irritability, symptoms shared with other depressive disorders. Additionally, patients show a significant increase in appetite and craving for foods high in carbohydrates which result in weight gain [3,9].

• **Post-partum depression (PPD):** This describes a heterogeneous group of depressive symptoms that affects mothers. These symptoms may surface before or after giving birth [10]. Half of the "postpartum" episodes begin before the time of delivery. Thus, are referred to collectively as "peri-partum" episodes. According to DSM-V [3] mood swings and anxiety symptoms during pregnancy, as well as the "baby blues" increase the risk for a postpartum major depressive episode.

• **Psychotic depression:** is a type of depressive disorder which is very severe and accompanied by psychotic symptoms [11,12]. It is commonly seen as a combination of psychosis and depression that is not separable into either of the two. Symptoms include psychotic features such as hallucinations or delusions. Other than its severity psychotic depression is associated with prolonged course, poor response to available drugs and higher relapse rate [9,13].

Epidemiology of depression

Depression is a major contributor to the global burden of disease and affects people in all communities across the world and 450 million people suffer from some type of mental or behavioral disorder [14]. The lifetime prevalence for major depression is reported to be as high as 14-17% and the one-year prevalence is 4-8%. The lifetime prevalence rates of MDD among women are 10-25%, and for men 5-12% [1,15].

Almost 10% of the total burden of disease in sub-Saharan Africa is attributed to neuropsychiatric disorders [16]. The lifetime prevalence of minor depressive disorder in Ethiopia was reported to be 2.2% [17]. Other studies conducted in Ethiopia showed the one-year prevalence of depression to be 4.4% among women [18]. The prevalence of depressive episodes was reported to be 9.1%. The major risk factors for these episodes were age, marital status, number of diagnosed chronic non communicable diseases and alcohol consumption [19]. Depression contributes about 6.5% of the burden of diseases in Ethiopia which is even higher compared to major infectious diseases such as Human Immunodeficiency Virus (HIV) infection [20]. Moreover, major depression and bipolar disorder were associated with three-fold increased risk of premature mortality as compared to the general population [17].

The prevalence of depression in children is relatively low (<1% in most studies), and then increases considerably all the way through adolescence with a one-year prevalence of 4–5% in mid to late adolescence. Depression in fact is major risk factor for suicide observed in adolescents; it's one of the leading causes of death in this age group Depression also leads to serious social and educational impairments and associated with an increased rate of smoking, substance abuse and obesity [21,22].

Pathophysiology of depression

Even though there are numerous studies attempting to shed light on the pathophysiology of depression, it still remains elusive. This is in fact the major reason for the slow paced drug development against this disease. There are diverse theories on the pathogenesis of depression most based on measurement of indirect markers, post-mortem studies and neuro-imaging techniques. For decades, depression pharmacotherapy and a resultant explanation for the underlying pathology, focused on the brain monoamine neurotransmitters level following the serendipitous discovery of imipramine and iproniazid as antidepressants [23,24].

A) Neural circuitry of depression: Various structural and functional studies report abnormalities in the areas of the brain that are responsible for the regulation of mood, reward response and executive functions. Post-mortem and neuro-imaging studies have reported morphological changes indicated by reductions in grey-matter volume and glial density in the prefrontal cortex and the hippocampus, regions that have received the most attention in animal research on depression. The decline in hippocampal function, which is believed to have an inhibitory effect on the hypothalamic-pituitary- adrenal (HPA) axis, could potentially be responsible for the hypercortisolemia seen in depression [24,25].

The mesolimbic dopamine system that consists of the nucleus accumbens (NAc) and the ventral tegmental area (VTA) also are believed to play a role in the pathogenesis of depression. These brain regions mediate the reward response to pleasurable stimuli such as food, sex and even drugs. Therefore, a peculiar lack of pleasure in depressed patients can possibly be explained as a dysfunction in this brain reward circuit [25]. Other studies have also shown a decrease in Locus coeruleus (LC) neuron density in some depressed and suicide population compared with controls [26].

B) Stress response circuits: Chronic stress and hyperactivity of the HPA axis (causing chronic hypercortisolemia) have been hypothesized to play a prominent role in the incidence of depression and even in recurrence after complete remission. Structural brain abnormalities have been documented in patients with elevated levels of corticosteroids. One of the brain structures affected is the amygdala, area of the brain involved in mainly regulating emotional reactivity and to some degree stress response [27,28]. Another brain region shown to decrease in size with chronic administration of corticosteroids is the hippocampus, area of the brain that is believed to exert an inhibitory signal to the HPA axis [29].

There is still a lack of complete understanding on how behavioral stress causes depression. However, chronic stress has been shown to alter the expression of genes regulating antioxidant systems, such as superoxide dismutases (SODs), catalase, glutathione peroxidase, glutathione reductase and NADPH oxidase. Moreover, animal studies uncovered that treatment with glucocorticoids cause elevation in the level reactive oxygen species (ROS) both *in vitro* and in the brains of animals, while also down-regulating various antioxidant enzyme and inducing depression-like behavior [30,31].

C) Genetic vulnerability and environmental interaction: There is now a compelling argument that in order for depression to surface there needs to be a complex gene-environmental interaction that alters an individual response to stressful life situations. No single gene polymorphism seems responsible for causing depression, it has been suggested that genetic factors make certain individuals susceptible to depression by increasing their vulnerability to stressful environmental factors [32].

A genetic polymorphism that has been perhaps a center of attention

for years is the allelic variation in the promoter region of the gene encoding the serotonin transporter (5- HTT). The promoter region of 5-HTT gene (5-HTTLPR) contains a functional polymorphism resulting in a long (L)/short(S) variant in the promoter region upstream of the transcription starting site. The short allele of 5-HTT has a low-activity and has been shown to put carriers at a greater risk of developing depression in response to stressful life events. This allele has also been related with poorer outcomes after antidepressant pharmacological and non-pharmacological treatments [33,34].

The rate-limiting enzyme in serotonin biosynthesis, tryptophan hydroxylase (TPH), is encoded by two distinct genes *Tphl* and *Tph2* and has been proposed to play a role in pathogenesis of depressive disorders and suicide. Single nucleotide polymorphisms (SNPs) on *Tph2* gene have been linked with increased incidence of MDD and completed suicide attempts. Also, *Tph l* gene, which is dominantly expressed in the pineal gland, is thought to influence suicidal risk by disrupting the synthesis of melatonin a hormone responsible for regulation of circadian rhythm resulting in an increase in suicidal risk [35,36].

A functional polymorphism, producing a valine to methionine substitution at the codon 66 (Val66Met) in the pro-BDNF region, has been identified in the BDNF gene, exhibiting a detrimental effect on intracellular trafficking and activity-dependent secretion and influencing hippocampal function, episodic memory and brain morphology. Healthy individuals with the BDNF Met variant display a low emotional stability and smaller hippocampus volume. Studies also suggest a complex interaction exists between the polymorphisms in genes encoding BDNF and 5- HTT to bring about a depressed phenotype [24,33].

D) The biogenic monoamine theory: The monoamine hypothesis of depression came into the picture after the serendipitous discovery of the first antidepressant drugs that were otherwise developed for other medical conditions. These clinical observations have contributed greatly to the understanding of the pathophysiological changes that take place in the brains of depressed individuals. The drugs were proposed to increase the amount of monoamine neurotransmitters in the brain either by blocking a monoamine degrading enzyme monoamine oxidase inhibitor (MAOI) or by blocking the reuptake of the neurotransmitters into the presynaptic neuron [37].

i) The Serotonin hypothesis: Serotonin is a monoamine neurotransmitter with a wide range distribution throughout the central nervous system. It is involved in physiologic activities such as pain sensation, appetite regulation, aggression and mood. Dysfunction in serotonergic system has been implicated in mood and anxiety disorders. The basis for this hypothesis is the fact that the first antidepressant drugs worked by reviving the diminished monoamine activity in the brain. And later SSRIs alone were found to be sufficient to treat symptoms of depression effectively. This fact further strengthened the involvement of 5-HT in the pathogenesis of the disease [38,39].

Subset of depressed patients have been reported to have a lowered level of 5-hydroxyindoleacetic acid (5-HIAA) a metabolite of 5-HT in the cerebrospinal fluid (CSF), which has been related to aggressive behavior and increased suicidal intent and impulsivity. The plasma level of the amino acid precursor (tryptophan) of 5- HT decreased and depressive symptoms can be induced in patients who are susceptible to depression by depleting this amino acid. Moreover, positron emission tomography (PET) imaging studies have reported a decrease in density of 5-HT_{1A} receptor subtype on depressed patients in different regions of the brain. There is also a decreased availability of 5-HTT in midbrain and brainstem regions. But this serotonergic dysfunction associated in depression is debated whether it is an etiologic factor or increases susceptibility [40,41].

ii) The catecholamine hypothesis: The catecholamine hypothesis of depression emerged in the 1960s after the observation that reserpine; an antihypertensive drug depletes central and peripheral amine storage in the nervous system, induced depression. However, there are no consistent findings on the alteration in the levels of NE metabolites in the CSF of depressed individuals. In subsequent years, the "supersensitivity hypothesis" was proposed which links depression to supersensitive presynaptic α_2R which is also supported by an increased density of these receptor types in post mortem studies, leading to an impaired NE activity [26,37].

Additionally, some symptoms of depression including anhedonia and psychomotor retardation are better explained by a derangement in the brain DA systems. These systems include the substantia nigra -basal ganglia motor system and the reward circuitry involving the NAc and VTA. There is a diminished DA activity in the NAc specifically which corresponds to the inability to experience pleasure which is one of the hallmarks of depression. The concentration of the dopamine metabolite homovanillic acid (HVA) in CSF is reported to be lower in depressed patients as well [42-44].

E) Inflammation and depression: The claim that depression is an inflammatory disorder is gaining popularity nowadays. This is supported by the fact that many pro-inflammatory marker levels are reported to be elevated in depressed patients. Examples of these markers are C-reactive protein (CRP), interleukin (IL)-6, IL-1 and tumor necrosis factor alpha (TNF-α). In fact depressive like behaviors can be induced in the laboratory by administration of (IFN)-α, a powerful inflammatory cytokine, that has also been shown to produce depression like symptoms in patients taking it for the treatment of hepatitis C [45,46].

An increase in reactive oxygen and nitrogen species generation and damage by oxidative and nitrosative stress (ONS), including lipid peroxidation, damage to deoxyribonucleic acid (DNA) and proteins is also seen. Even though a complete understanding of the mechanisms involved remains obscure, an increase in pro- inflammatory cytokines results in a lack of neuronal plasticity and eventual neurodegeneration. Also pro-inflammatory cytokines can interfere with the activity of growth factors which results in reduced neurogenesis as the immune changes can damage glial cells and neurons [47,48].

Neurothrophic hypothesis: Significant atrophy of certain prefrontal cortex areas and hippocampus observed in depression as well as decreased levels of nerve growth factors (NGF) such as BDNF has led to the neurotrophic hypothesis. BDNF is an important molecular regulator of neuronal development and plasticity. It increases survival of neurons, stimulates the growth of dendrites and increases the spine density and also involved in maturation of excitatory synapses, processes that are important in learning and adaptation process which seems to be deficient in depression [33,49,50].

The expression of BDNF is believed to be halted by chronic stress and normal level of this growth factor is attained after a successful treatment with antidepressants. This is consistent with the fact that antidepressants take at least 2-3 weeks to elicit their actions, possibly through causing a longer lasting neuroadaptive changes in the brain rather than a simple increase in the level of neurotransmitters. This neuroadaptive change includes the process of neurogenesis, a phenomenon recently revealed to also occur in specific areas such as

the subventricular and subgranular zones of the dentate gyrus giving rise to neurons in the hippocampus. This process includes cell division, migration and differentiation medicated by NGFs [51-53].

Vascular endothelial growth factor (VEGF) is another NGF that promotes proliferation of neuronal cells in some brain regions like the hippocampus. It achieves this by activating intracellular signaling cascades that involves mitogen-activated protein kinase (MAPK) pathway. This signaling pathway has also been postulated to underlie the late antidepressant response of currently available drugs. This is achieved through the activity of gene transcription inducer cyclic AMP response element Binding protein (CREB) which is activated by MAPK resulting in stabilization of synaptic plasticity [54,55].

F) Neuropeptides and depression: There is increasing evidence that this neuropeptides are involved in the modulation of stress- related behaviors and mood by acting on neurokinin type-1 receptors (NK-1). Substance P (SP) is one of these neuropeptides known for its wide spread distribution in the brain and its co-localization with 5-HT and NE neurons [56]. Elevated CSF SP concentrations have been reported in depressed patients and patients with PTSD after exposure to a stressful stimulus. Additionally, central administration of SP has been shown to induce stress response. This is supported by the antidepressant activity of NK-1 antagonists [57,58].

G) Hormones and depression

i. Thyroid hormones: Thyroid hormones (TH) imbalances are implicated in the pathophysiology of neurodegenerative and psychiatric conditions. These hormones are very essential for brain development, maturation and have been shown to promote neurogenesis, in particular, in the hippocampus [59]. Hypothyroidism has been linked to depressive -like behavior in that it impaired hippocampal neurogenesis which resolved with hormone replacement. Animal studies also revealed that thyroid hormone causes an increase in seretonergic neurotransmission which supports the fact that TH supplementation has been beneficial in management of refractory cases of depression [60,61].

ii. Estrogen involvement: Increased female susceptibility to depression mostly overlaps periods of low estrogen levels in the menstrual cycle, postpartum and after the onset of menopause. Animal studies indicate mood enhancing actions of estrogen as well as synergy with monoaminergic drugs. Estrogen enhances mood by increasing the rate of degradation of MAO and intraneuronal 5- HT transport, causing an overall increase in 5-HT availability in the synapse. In addition serotonergic neurotransmission, estrogen also is believed to have modulatory effect on hippocampal neurogenesis, BDNF signaling, and HPA axis function [62,63].

iii. Vasopressin and depression: Arginine vasopressin (AVP) is a hypothalamic hormone that influences some key symptoms pertinent to major depressive disorder. Its level is reported to be elevated in patients suffering from this mental disorder [64]. AVP has been linked to play a role in the regulation of stress response, one of the prominent features of depression, in that it synergizes with CRF at the level of the pituitary to influence the release of ACTH [65]. Elevated AVP concentrations were also associated with psychomotor retardation in patients with major depressive disorder [66].

H) Implications of the circadian rhythm in depression: Melatonin, a hormone secreted by the pineal gland, in a circadian fashion, regulates the rhythm of various biological parameters like body temperature, cortisol secretion, and sleep cycles by acting on receptors in the suprachiasmatic nucleus (SCN) of the hypothalamus [67]. Delayed circadian rhythm in patients with depression has been linked to diminished level of melatonergic signaling in the brain. Patients may manifest with delayed onset of sleep, difficulty in maintaining sleep and early morning awakening. This has given way to the discovery of new antidepressant agent, agomelatin, which acts on melatonin and serotonin receptors on the SCN. Disruption of circadian rhythm has also been proposed to make individuals susceptible to depression [68-70].

Management of depression

An array of treatment options has been developed to combat depression over the decades. The various approaches include pharmacotherapy, psychotherapy and somatic therapy often employed for treatment resistant depression [58].

Pharmacotherapy: The first antidepressants were discovered by serendipity, following incisive clinical observations that iproniazid, a drug developed for the treatment of tuberculosis, showed mood elevating effects. Just as well, imipramine, an alleged antipsychotic drug showed antidepressant activity. These observations not only led the way for subsequent studies to develop the first groups of antidepressant drugs MAO inhibitors and TCAs, but also have contributed immensely to the pathophysiological understanding of depression as we know it today [71,72].

Majority of the available antidepressant drugs work by modulating the brain monoamine neurotransmission. The primary mechanism of these drugs is increasing the overall synaptic concentration of monoamines (serotonin, norepinephrine and dopamine). They achieve this either by blocking their reuptake into the presynaptic neuron by binding to the respective neurotransmitter transporter or through inhibition of the monoamine degrading enzyme MAO reversibly or irreversibly [58]. Certain antidepressants also act on presynaptic or postsynaptic neurotransmitter receptors to alter the neurotransmission. There also atypical antidepressant drugs that are emerging in the market. This list includes antipsychotics, NK-1 antagonist, GR antagonists and melatonergic drugs [56,73,74].

As mentioned earlier, there is a time delay on the onset of the response after treatment with antidepressants. It is believed that long term neuronal adaptations may underlie the effects rather than the acute modulation of transporters or receptors that alter the neurotransmission. Repetitive activation of the neurons by these drugs is believed to result in changes such as synaptic plasticity, axonal sprouting, neurite extension, and promotion of cell survival cue brought about by complex cellular signal transduction mechanisms involving neurotrophins and various transcription factors [72].

Somatic therapy: Somatic therapy for depression is a device-based approach that consists of introducing transient electric or magnetic current onto the scalp or to anatomically deep brain structures. The use of this approach is favored in the management of depression refractory to the available drugs. It also has a wide applicability for maintenance of effect after successful remission as well as can be used as an add-on therapy. The various somatic treatments are believed to induce transient seizures that are responsible for the clinical effects. The mechanism of action is largely attributed to increasing the level of neurotransmitters and sensitization of post synaptic receptors through changing the neuronal firing in the regions involved. There is also the participation of growth factors and induction of long lasting neuronal adaptation [75].

ECT on neurotransmitters, receptors, and postreceptor signaling

mechanisms in the brain, particularly those that are implicated in the mechanism of action of antidepressant drugs. The emphasis has been primarily on serotonergic, noradrenergic, and dopaminergic systems with some consideration of γ-aminobutyric acid (GABA)-ergic and more recently glutamatergic mechanisms. Electrophysiological studies suggest that an important effect of ECT on brain serotonergic systems in rodent brain is sensitization of postsynaptic serotonin (5-HT)1A receptors and a consequent increase in serotonergic transmission offers relationship between chemical and electric transmission of signals in the brain Increase in hormonal levels such as TSH**.**

i) Electroconvulsive therapy: Electroconvulsive therapy (ECT) is the first effective somatic therapy to be used for the treatment of mental disorders with a widespread clinical use even up to now. Basically a seizure is induced by applying an electric current with pulse width from 0.3 to 1msec, frequency from 20 to 120 Hz, duration of the stimulus 0.5-8 sec to the surface of the head. This procedure requires the patients to be properly anesthetized before the actual session to avoid any serious complications [76]. ECT is believed to cause increased blood level of norepinephrine and causes sensitization of 5-HT_1A receptors [54,77].

ii) Transcranial magnetic stimulation: Transcranial magnetic stimulation (TMS) is another type of somatic treatment option for treatment resistant depression. TMS induces depolarization of cortical neurons by the use of magnetic current that passes through a metal coil applied to the scalp of the patient, making it non- invasive [33,77]. TMS results in elevated levels of dopamine and serotonin. It also causes up regulation of β-adrenergic and 5HT receptors in the frontal cortex. There are also reports of subsensitivity of presynaptic serotonergic autoreceptors observed after receiving TMS [76].

iii) Vagus nerve Stimulation: Vagus nerve stimulation (VNS) is a minimally invasive procedure where an impulse generator device is implanted in the chest area of the patient attached to the left vagus nerve with lead wires. The clinical effects of VNS treatment do not surface soon after treatment therefore making it a less appealing choice for managing acute treatment resistant depression. The mechanism of action of VNS remains elusive [77,78].

Medicinal plants used to treat depression: Medicinal plants around the world have been used to treat disorders of the body and the mind since antiquity. Herbal medicine has been a reasonable alternative for the management of mental disorders such as anxiety, depression and dementia among plenty others [79]. Developing antidepressants from herbal sources seems to be reasonable approach due to their therapeutic efficacy and lower incidence of side effects [6]. *Hypericum perforatum* commonly known as St. John's wort is the only herbal antidepressant that has been approved for the clinical management of mild to moderate cases of depression. Hypericin and hyperforin are flavonoids present in hypericum that are claimed to be responsible for the antidepressant activity of the plant [80].

Medicinal plants most widely used to treatment depression around the world are *Hypericum perforatum, Centella asiatica*, *Rhodiola rosea*, *Pfaffia paniculata*, *Rauwolfia serpentina*, *Rhododendron molle*, *Schizandra chin*, *Thea sinensis*, *Uncaria tome*, *Valeriana officinalis* and *Withania somnifera* [5,81,82]. There is a long history of using plants for treating many diseases in Ethiopia. This herbal based therapy is most valued and has been passed from generation to generation by word of mouth. Herbal therapy still remains to be the first line treatment option for nearly 80% of the population. Plants such as *Justicia odora*, *Whitiana somnifera*, *Calpurnia aurea* and *Asparagus leptocladodius* have traditionally been used for the treatment of depression [83,84].

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