Modulations of Mammalian Brain Functions by Antidepressant Drugs: Role of Some Phytochemicals as Prospective Antidepressants

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Introduction

Depression is the most common form of mental illness. It is a state of low mood that can affect a person’s thoughts, feelings, behavior and senses of a well-being, disturbed sleep, typically with early morning awakenings, leading to decrease in sleep duration and seasonal affective disorder [1-4]. The cause of depression could be Adversity in childhood, such as bereavement, unequal parental treatment of siblings, neglect, sexual abuse, life events include job problems, financial difficulties, a medical diagnosis, bullying, relationship troubles, separation, natural disasters, catastrophic injury, social isolation, jealousy, loss of a loved one, childbirth, and menopause [5-9] and resulting changes significantly increases the depression. Adolescents may be more prone to experiencing depressed mood [10].

The symptoms of depression which are observed today were recognized in ancient times. The ancients were also recognized a large overlap of depression with anxiety and excessive alcohol consumption, both of which are well established today. It is likely that many brain regions mediate the diverse symptoms of depression. While many brain regions have been implicated in regulating emotions, we still have a very rudimentary understanding of the neural circuitry underlying normal mood and the abnormalities in mood that are the hallmark of depression. This lack of knowledge is underscored by the fact that even if it were possible to biopsy the brains of patients with depression, there is no consensus in the field as to the site of this pathology and hence the best brain region to biopsy. However, studies of the brains of depressed patients obtained at autopsy have reported abnormalities in many of these same brain regions. Knowledge of the function of these brain regions under normal conditions suggests the aspects of depression to which they may contribute. Given the prominence of so-called neurovegetative symptoms of depression, including too much or too little sleep, appetite, and energy, as well as a loss of interest in sex and other pleasurable activities, a role for the hypothalamus has also been speculated.

On the basis of severity of depression, it can have several forms: Major depression is characterized by appearance of severe symptoms that interfere with your ability to work, sleep, study, eat, and enjoy life. Persistent depressive disorder occurs in a person diagnosed with persistent depressive disorder may have episodes of major depression along with periods of less severe symptoms, but symptoms must last for 2 years. Psychotic depression occurs in a person who has severe depression plus some form of psychosis, such as having disturbing false beliefs or a break with reality, or hearing or seeing upsetting things that others cannot hear or see. Postpartum depression is much more serious than the "baby blues" that many women experience after giving birth, when hormonal and physical changes and the new responsibility of caring for a new-born can be overwhelming. It is estimated that 10 to 15 per cent of women experience postpartum depression after giving birth. Seasonal affective disorder (SAD) is characterized by the onset of depression during the winter months, when there is less natural sunlight. The depression generally lifts during spring and summer. SAD may be effectively treated with light therapy, but nearly half of those with SAD do not get better with light therapy alone. Antidepressant medication and psychotherapy can reduce SAD symptoms, either alone or in combination with light therapy. Bipolar disorder is also called as manic-depressive illness. It is characterized by cycling mood changes from extreme highs (e.g., mania) to extreme lows (e.g., depression).

Many women face the additional stresses of work, home responsibilities, caring for children, aging parents, abuse, poverty, and relationship strains. Women’s higher depression rate may be linked to

**Keywords:** Depression; Brain functions; Antidepressant drugs; Antipsychotic plants; Herbal ingredients; Prospective antidepressants; Psychotherapies

Abstract

Depression in the form of serious mental illness is known to influence overall physiological and cognitive functions of any individual. Existing reports suggest that many brain regions mediate the diverse symptoms of depression but exact root cause of this illness is not yet known. However, several biochemicals, molecular and genetic bases have been found to be associated with brain disorders leading to depression. People with depression can best be treated with medications, psychotherapies, and other viable methods. The most commonly used antidepressants are the serotonin reuptake inhibitors (SSRIs), serotonin-nor-epinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), tetracyclic antidepressants (TeCAs), buprenorphine and nor-adrenergic and specific serotonergic antidepressant (NaSSAs) but most of them possess serious side effects in patients. The present review article illustrates an updated account of our understanding about the molecular constituents of the different regions of the brain that control the physiological and behavioural functions of a person, mechanisms of actions of currently available antidepressants and their side effects, if any, as well as the prospects of using phytochemicals as safe and effective alternative medicines.

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**Introduction**

Depression is the most common form of mental illness. It is a state of low mood that can affect a person's thoughts, feelings, behavior and senses of a well-being, disturbed sleep, typically with early morning awakenings, leading to decrease in sleep duration and seasonal affective disorder [1-4]. The cause of depression could be Adversity in childhood, such as bereavement, unequal parental treatment of siblings, neglect, sexual abuse, life events include job problems, financial difficulties, a medical diagnosis, bullying, relationship troubles, separation, natural disasters, catastrophic injury, social isolation, jealousy, loss of a loved one, childbirth, and menopause [5-9] and resulting changes significantly increases the depression. Adolescents may be more prone to experiencing depressed mood [10].

The symptoms of depression which are observed today were recognized in ancient times. The ancients were also recognized a large overlap of depression with anxiety and excessive alcohol consumption, both of which are well established today. It is likely that many brain regions mediate the diverse symptoms of depression. While many brain regions have been implicated in regulating emotions, we still have a very rudimentary understanding of the neural circuitry underlying normal mood and the abnormalities in mood that are the hallmark of depression. This lack of knowledge is underscored by the fact that even if it were possible to biopsy the brains of patients with depression, there is no consensus in the field as to the site of this pathology and hence the best brain region to biopsy. However, studies of the brains of depressed patients obtained at autopsy have reported abnormalities in many of these same brain regions. Knowledge of the function of these brain regions under normal conditions suggests the aspects of depression to which they may contribute. Given the prominence of so-called neurovegetative symptoms of depression, including too much or too little sleep, appetite, and energy, as well as a loss of interest in sex and other pleasurable activities, a role for the hypothalamus has also been speculated.

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Many women face the additional stresses of work, home responsibilities, caring for children, aging parents, abuse, poverty, and relationship strains. Women's higher depression rate may be linked to
biological life cycle, psychosocial, and hormonal factors that a women experience. Women may also have a severe form of premenstrual syndrome (PMS) called premenstrual dysphoric disorder (PMDD). During the transition into menopause, women experience an increased risk for depression in addition with that; osteoporosis may also be associated with depression.

Men are more likely to be very tired, irritable, lose interest in once-pleasurable activities, frustrated when discouraged, irritable, angry, and sometimes abusive and have difficulty in sleeping. When men are depressed they may more likely turn to alcohol or drugs. Some men throw themselves into their work to avoid talking about their depression with family or friends, or behave recklessly.

When older adults do have depression, it may be overlooked. They may be less likely to experience feelings of sadness. Older adults may also have more medical conditions such as heart disease, stroke, or cancer, which may cause depressive symptoms. They may be taking medications with side effects that contribute to depression. Some older adults may experience vascular depression, or sub-cortical ischemic depression also called arteriosclerotic depression. Those with vascular depression may have risk for, co-existing heart disease. Older adults with depression improve when they receive treatment with an antidepressant, psychotherapy, or a combination of both.

Children who develop depression often have episodes. Childhood depression often persists, recurs, and continues into adulthood, if left untreated. Depression during the teen years comes at a time of great personal change a when boy or a girl is forming an identity apart from their parents and emerging sexuality for the first time in their lives. Before puberty, boys and girls are equally developing depression. However, girls are twice as likely as boys to have a major depressive episode. A child with depression may pretend to be sick, refuse to go to school, cling to a parent, or worry that a parent may die. Older children may get into trouble at school, be negative and irritable, and feel misunderstood. It can also lead to increased risk for suicide. It may be difficult to accurately diagnose a young person with depression, because the signs may be viewed as normal mood swings of children as they move through developmental stages.

Thus, we are interested in understanding the molecular constituents of the brain’s reward regions that control the functioning of these circuits under normal conditions as well as the molecular changes that drugs and stress induce these circuits that contribute to symptoms of addiction and depression. People with depression can get better with treatment by medications, psychotherapies, and other methods can effectively treat people, even those with the most severe depression.

Scientific Bases of Depression

Molecular and genetic bases of depression

Genes coding for neurotransfactors and brain signaling molecules which play regulatory roles in many neuronal functions are, brain-derived neurotrophic factor (BDNF) and 5-hydroxytryptamine (5 - HT). These two factors are two different signaling molecules functioning in separate but overlapping pathways and play regulatory role in functions, like neuronal survival, neurogenesis, synaptic plasticity and regulation of depression.

BDNF and its receptors are a widely distributed neurotrophin found in the brain and were first isolated as a secretory protein [11,12]. Its gene has a complex structure with several isoforms [13,14]. The promoters of individual BDNF transcripts are regulated by various physiological factors [15-17]. BDNF function is mediated through the receptor systems, p75 neurotrophin (p75NTR) and tropomyosin-receptor kinase beta (Trkβ). These receptors are present on membrane of intracellular vesicles in the absence of signals and their presence enhances the specificity of Trkβ for the primary ligand, BDNF [18-23]. The level of cAMP, electrical activity, and Ca++ ion stimulate exocytosis of these cytoplasmatic vesicles into the cell surface, releasing Trkβ on the outer membrane with other receptors [24,25]. After binding with BDNF Trkβ dimersizes and is autophosphorylated at several tyrosine residues [26]. Phosphorylation of tyrosine at position 490 in Trkβ activates phosphatidylinositol 3 kinase (PIK3) which through Akt1/2 increases transcription of Bcl - 2, and Bax which is responsible for neuronal survival. Phosphorylation of tyrosine at position 785 of Trkβ recruits phospholipase C-γ1 (PLC-γ1) [27] which hydrolyses phosphatidylinositol 4,5-bisphosphate, generating inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 promotes Ca++ release from endoplasmic reticulum and also activates protein kinase C (PKC) and Ca++-calmodulin regulated protein kinase. PKC is required for neurotrophic growth factor (NGF), activates Erk1 and Erk2 [28]. Activation of Erk / MAPK-Ras signaling cascade is essential for neurotrophin-promoted differentiation of neurons [29,30].

Depression is characterized by two events: behavioral despair and the inability to experience pleasure. These behaviors are controlled by two interacting brain systems: the brain stress system by HPA pathway and the brain reward system via ventral tegmental area-nucleus accumbens (VTA - NAc) and VTA prefrontal cortex. VTA - NAc is the origin of dopaminergic neurons. The dopaminergic VTA-NAc pathway plays a crucial role in reward and motivation. The effects of BDNF on these two systems have been shown experimentally. The BDNF produces anti-depressive effects through hippocampal infusion [31,32]. It appears to play a prodepressive role in the VTA-NAc reward system [33]. Berton et al., has shown that mice with wild-type BDNF showed social withdrawal, while mice with BDNF gene deletion prevented social defeat, similar to the effect seen with chronic antidepressant treatment by repeated exposure to aggression. It has also been found that neural progenitor cells failed to produce antidepressant-induced proliferation and neurogenesis in mice lacking hippocampal Trkβ [34,35]. BDNF has been reported to regulate the transmission at GABAergic and glutamatergic synapses by presynaptic and postsynaptic mechanisms [30,36]. The more detailed investigation on the effects of BDNF manipulations on behavior related to anhedonia and motivation, and despair and stress is needed.

5-HT/serotonin regulate a wide range of functions such as behavior, cognition and mood. There are 15 genes which have been reported for encoding 5-HT receptors in mammalian brain and all of them are G-protein coupled receptors, except ionotropic 5 - HT3 [37]. The 5 - HT is removed by 5-hydroxytryptamine transporter (5 - HTT) of the presynaptic neurons from synaptic cleft. It has been reported that the longer duration serotonin present in synaptic cleft longer the activation, which lead to depression [38], 5-HTT is encoded by a single gene SLC6A4 and has a polymorphism (5 - HTTLPR) in 5-HTT promoter region [39]. This abnormal 5 - HTTLPR signaling has been shown to be associated with anxiety, depression and suicides [38,40-44]. It has been found that unipolar depression is associated with diminished serotogenic function that lead to warping in cognitive processing and emotions [45,46]. Studies in preschoolers have been reported a correlation between BDNF and 5 - HTTLPR polymorphisms in development of brain and shown high level of cortisol which may be a cause of depression [47]. However, studies in
adolescents have been shown to be more involved in depression [46,48]. In India, studies in adults aged 40–50 years found that homozygous individuals with the short (s / s) variant showed a poor treatment response to the escitalopram [49]. Besides BDNF and 5-HTTLPR, a few of the top prioritized gene products are presented below and several of them are listed in Table 1.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Susceptible variants</th>
<th>Location</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonergic SLC6A4</td>
<td>14-16 repeats upstream to transcript initiation site</td>
<td>17q11.2</td>
<td>Serotonin transporter</td>
<td>[42,48]</td>
</tr>
<tr>
<td>HTR1 A</td>
<td>rs6295 rs878567</td>
<td>5q11.2-q13</td>
<td>Serotonin receptor subfamily</td>
<td>[50-52]</td>
</tr>
<tr>
<td>HTR2A</td>
<td>rs6311 rs6313</td>
<td>13q14.2</td>
<td>Serotonin receptor</td>
<td>[53,54]</td>
</tr>
<tr>
<td>TPH2</td>
<td>rs4570626</td>
<td>12q21.1</td>
<td>Rate limiting enzyme in serotonin biosynthesis</td>
<td>[55-57]</td>
</tr>
<tr>
<td>Dopaminergic DBH</td>
<td>rs6271 rs5320</td>
<td>9p34</td>
<td>Enzyme converting dopamine to nor epinephrine</td>
<td>[58-60]</td>
</tr>
<tr>
<td>DRD2</td>
<td>Rs6277</td>
<td>11q22-23</td>
<td>Dopamine G-coupled receptor inhibits adenyl cyclase activity</td>
<td>[61]</td>
</tr>
<tr>
<td>DRD4</td>
<td>C616G C521T</td>
<td>11p15.5</td>
<td>Dopaminergic D4 receptor</td>
<td>[62]</td>
</tr>
<tr>
<td>Neurotrophin BDNF</td>
<td>rs6265</td>
<td>11p13</td>
<td>Protein involved in brain development</td>
<td>[63,64]</td>
</tr>
<tr>
<td>NGFR</td>
<td>rs2072446</td>
<td>17q21-22</td>
<td>Trk receptor</td>
<td>[65]</td>
</tr>
<tr>
<td>Other COMT</td>
<td>rs4680</td>
<td>22q11.21</td>
<td>Enzyme degrading catecholamines</td>
<td>[66-68]</td>
</tr>
<tr>
<td>GNB3</td>
<td>rs5443</td>
<td>12p13</td>
<td>G-protein involved in signal transduction</td>
<td>[69-71]</td>
</tr>
<tr>
<td>DTNBP1</td>
<td>rs760761 rs26019522</td>
<td>6p22.3</td>
<td>Important for biosynthesis of lysozyme related organelles</td>
<td>[72-74]</td>
</tr>
<tr>
<td>MAO-A</td>
<td>rs1137070</td>
<td>Xp11.3</td>
<td>Mitochondrial enzyme catalyzing oxidative deamination of amines</td>
<td>[75]</td>
</tr>
<tr>
<td>MTHFR</td>
<td>rs1801133</td>
<td>1p36.3</td>
<td>Folate and homocysteine Metabolism</td>
<td>[76-79]</td>
</tr>
<tr>
<td>GRIA3</td>
<td>rs687577</td>
<td>3q11.9</td>
<td>Neuronal development</td>
<td>[80]</td>
</tr>
<tr>
<td>APOE</td>
<td>Epsilon-4</td>
<td>19q13.2</td>
<td>Associated with the late life depression including Alzheimer’s and Parkinson’s diseases etc.</td>
<td>[81,82]</td>
</tr>
<tr>
<td>FBKP5</td>
<td>rs9296158</td>
<td>12p13.33</td>
<td>Protein folding and trafficking</td>
<td>[83-85]</td>
</tr>
</tbody>
</table>

Table 1: Important variants of different genes involved in stress and depression.

FK506-binding proteins 5 (FKBP5) plays role of immunoregulation, protein folding, trafficking and interacts with HSP90, P23 and mature corticoid receptors such as progesterone, glucocorticoid, mineralocorticoid receptors. SNPs of FBKP5 (rs9296158, rs3800373, rs1360780 and rs9470080) have been shown to be associated with childhood trauma [83]. It was also reported that this protein is associated with higher rate of depressive disorders [85,86]. An increased level of FBKP51 can be correlated with anxiety phenotype and therefore, efforts to discover a drug has been focusing on depleting FBKP51 levels, which may yield novel antidepressant therapies [87].

Biochemical basis of depression

Dopamine β-hydroxylase (DBH) catalyses a key step in biosynthesis of nor-adrenaline from dopamine. The low activity of DBH has been correlated [88,89] and may be considered as a biomarker of depression.

Tumor necrosis factor (TNF) plays an important role in modulating neuronal and immune interactions. The studies reported that pro-inflammatory cytokines (TNF - alpha) and interleukins (IL6 and IL10) were increased in patients with depression [90-92]. Receptors of IL, tachykinin receptors NK1 and NK2 expressed in monocytes are increased in major depression and may be considered as biomarkers.

Glycogen synthase kinase 3β (GSK3β) plays an important role in mood stabilization, and is also involved in neural cell development and
energy metabolism. GSK3β has been reported to be involved with depression [93,94].

Tryptophan hydroxylase 2 (TPH2) is a rate-limiting enzyme of serotonin biosynthesis, which catalyses the conversion of tryptophan to 5 - hydroxytryptophan (5 - HTP). TPH2 has been shown to be associated with the several depressive disorders such as depression-associated personality traits, anxiety, bipolar disorder, aggression, and suicide, deficits in cognitive control and emotion and attention deficit hyperactivity disorder [95]. TPH2 variant (rs120074175) has been shown to be associated with depression [96], but studies in further years failed to establish this association [97-99]. TPH1, an isoform of TPH2 expressed in the gastrointestinal tract and pineal gland [100], has been reported that rs2108977 of TPH1 is associated with hyperphagia, posttraumatic stress disorder (PTSD), higher level of anxiety and depression.

Catechol-O-methyltransferase (COMT) degrade catecholamine, like dopamine, epinephrine and nor-epinephrine, therefore it is involved in the inactivation of catecholamine neurotransmitters. An SNP of COMT, rs4680 corresponds to Val108Met (soluble form) and Val158Met (membrane bound form) [101,102]. rs4680 has been reported to be associated with bipolar disorder, obsessive compulsive disorder, schizophrenia, major depressive disorder, and Parkinson's disease. These indices however could be exploited as suitable targets to develop effective antidepressants [67,103-106].

The mammalian brain has many specialized brain systems that work across specific regions under depression. Some of the most studied regions are listed in Table 2.

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Normal function</th>
<th>How it is associated</th>
<th>Abnormal function</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala</td>
<td>brain's fear hub which activates our natural fight-or-flight response</td>
<td>Amygdala helps create memories of fear and safety, may help to improve treatments for anxiety disorders like phobias or post-traumatic stress disorder (PTSD).</td>
<td>Reduced ACC activity has been linked to disorders such as ADHD, schizophrenia, and depression.</td>
<td></td>
</tr>
<tr>
<td>Prefrontal cortex (PFC)</td>
<td>the brain's executive functions, such as judgment, decision making, and problem solving, PFC is involved in using short-term working memory and in retrieving long-term memories, also helps to control the amygdala during stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate cortex (ACC)</td>
<td>controlling blood pressure and heart rate, sense a mistake, feel motivated, stay focused on a task, and managing emotions</td>
<td>may be involved in mood disorders through its control of a major mood circuit called the hypothalamic-pituitary-adrenal (HPA) axis</td>
<td>When damaged it can't create new memories, but can still remember past events and learned skills, and carry on a conversation, all which rely on different parts of the brain</td>
<td>[107-115]</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>helps to create and file new memories</td>
<td>involved in high level cognitive functions such as maintaining and using information in working memory, problem solving, and decision making</td>
<td>common in most major psychiatric and neurological disorders, including depression</td>
<td></td>
</tr>
<tr>
<td>Central executive network</td>
<td>usually active during specific tasks probed in cognitive science</td>
<td>dysfunctions have been characterized by major depression</td>
<td></td>
<td>[116-119]</td>
</tr>
<tr>
<td>Default mode network</td>
<td>involved in detecting and orienting the most pertinent of the external stimuli and internal events being presented</td>
<td>negative emotional states show an increase in the right anterior insula during decision making events if the decision has already been made</td>
<td>high activity in the right anterior insula is thought to contribute to the experience of negative and worrisome feelings</td>
<td>[107,116,120,121]</td>
</tr>
</tbody>
</table>

Table 2: Some of the most studied specific regions of mammalian brain associated to depression.

**Antidepressants and their Mechanism of Action**

Antidepressants are used for the treatment of depression including dysthymia, anxiety, obsessive compulsive disorder, eating disorders, chronic pain, neuropathic pain, dysmenorrhoea, snoring, migraines, attention-deficit hyperactivity disorder (ADHD), and sleep disorders [122]. The most important antidepressants are the selective serotonin reuptake inhibitors (SSRIs), serotonin-nor-epinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), tetracyclic antidepressants (TeCAs), and nor-adrenergic and specific serotonergic antidepressant (NaSSAs).
Other drugs used or proposed for the treatment of depression include bupropion and St John's wort [123-125].

Some of the most popular antidepressants are called selective serotonin reuptake inhibitors (SSRIs). Some of the most prescribed SSRIs for depression are fluoxetine, sertraline, escitalopram, citalopram and paroxetine. Serotonin and nor-epinephrine reuptake inhibitors (SNRIs) include venlafaxine (Effexor) and duloxetine (Cymbalta). SSRIs and SNRIs can produce headaches, nausea, jitters, or insomnia when people take them. Some people also experience sexual problems with SSRIs or SNRIs. Bupropion that works on dopamine tends to have similar side effects as SSRIs and SNRIs, but it is less likely to cause sexual side effects. However, the risk for seizures of a person can increase.

Tricyclics include imipramine and nortriptyline, are old and powerful antidepressants. They are not used as much today because of their more serious side effects. They may affect the heart, dizziness, drowsiness, dry mouth, and weight gain especially in older adults. They may be dangerous if taken in overdose. These side effects can usually be corrected by changing the dosage or switching to another medication.

Monoamine oxidase inhibitors (MAOIs) can be effective when a person experiences increased appetite and the need for more sleep. MAOIs may help with anxious feelings and other specific symptoms. However, people who take MAOIs must avoid certain foods and beverages that contain a substance called tyramine, certain medications, including some types of birth control pills, prescription pain relievers, cold and allergy medications, and herbal supplements. These substances can interact with MAOIs to increase blood pressure, increased sweating, seizures, hallucinations, muscle stiffness, confusion and other life-threatening conditions.

Augmentation and Combination Strategy

This strategy involves use of different antidepressant drugs in suitable combinations. This strategy has been used to combat SSRI associated fatigue [126]. This strategy has an evidence for the adverse effects although it may be used in clinical practices [127]. The American Psychiatric Association guidelines suggest augmentation, which includes lithium and thyroid augmentation, sex steroids, dopamine agonists, glucocorticoid-specific agents [128].

Modulations in Mammalian Brain by Antidepressant Drugs

Basically antidepressants work in two ways

1. Block reuptake of serotonin
2. Block degradation of serotonin by inhibiting monoamine oxidase [129,130]. For the treatment of depression and anxiety, serotonin and nor-epinephrine reuptake inhibiting drugs (SRIs) has been used [129-134]. Hence, the amount of serotonin and nor-epinephrine increases over a period of time, and help in improving mood and reducing anxiety. In rodents, it has been reported that increase in the transcript level of BDNF in hippocampus and cortex region of brain following antidepressant treatment [135,136].

Some studies have reported the direct incorporation of BDNF in hippocampus of rodents which mimics antidepressant treatment [137,138]. On the other hand, another study on BDNF knock down mice reported that they did not respond to antidepressants and also did not show depressive behaviour [139]. However studies in humans with antidepressant treatment have also been reported an increased BDNF level [140-142]. Fluoxetine (selective serotonin reuptake inhibitor), administration enhanced neurogenesis and expression of BDNF, which resulted into the enhancement of long term potentiation (LTP) [143,144]. The Val66Met polymorphism in BDNF showed interference with SSRI and neurogenesis [145]. However, the exact molecular mechanism of neurogenesis mediated by BDNF is not understood [146]. Antidepressants alter the expression of CAMP response element binding protein (CREB), which gets activated by phosphorylation. CREB protein activates – cAMP-pkA pathway, Calciummodulin pathway, and MAP-K pathway [147]. It has also reported that BDNF acts through CREB pathway [148,149]. Mouse with over expression of CREB showed decreased depressive behaviour [150].

The decreased hippocampal BDNF level has been correlated with stress-induced depressive behaviours [151-155] and treatment with antidepressant(s) enhanced BDNF expression [151,155,156]. In mature neurons the long lasting epigenetic modifications have been shown and reported that it may be implicated in complex neurological disorders [157]. The methylation of histone of DNA can be regulated by stress resulting in down regulation of BDNF III and IV transcripts. However, histone demethylase can also down regulate BDNF transcripts but when antidepressants administered, it promotes histone acetylation and down regulates histone deacetylation [158]. Factors associated with depression mentioned in Figure 1.

Psychotherapy

Psychotherapy may be the best option for the treatment of mild to moderate depression. However, it may not be enough so, a combination of medication and psychotherapy may be the most effective approach to treat major depression and reducing the chances of it coming back. In addition to application of drugs, several types of psychotherapy practices may help people suffering from depression. Cognitive/behavioral therapy (CBT) helps people with depression to re-structure their negative thoughts in a positive and realistic way. It may also be used to recognize things that may be contributing to the depression. Interpersonal therapy (IPT) helps people to understand and work through troubled relationships that may cause depression. Electroconvulsive therapies (ECT), formerly known as “shock therapy” may be useful in which medication and/or psychotherapy does not relieve.

Treatment of depression with antipsychotic plants / Herbal treatment

The plants proved to have antidepressant property are listed as following: Apocynum venetum, Areca catechu, Cimicifuga racemosa,
Centella asiatica, Clitoria ternetea, Hypericum perforatum, Crocus sativus, Bacopa monnieri, Mangolia officinalis, Curcuma longa, Mimosa pudica, Ginkgo biloba, Ocimum sanctum, Rhazya stricta, Rhizoma acori tatarinowii, Piper methysticum, Withania somnifera, Siphocampylus verticillatus, Oenothera biennis, Morinda officinalis and Perilla frutescens [159]. Their detailed chemical characteristics and antidepressant potential have been summarized in Table 3.

<table>
<thead>
<tr>
<th>Plant name</th>
<th>Antidepressant activity shown by the chemical compound present</th>
<th>Part of Plant used</th>
<th>Mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apocynum venetum</td>
<td>might be due to flavinoids such as hyperoside and isoquercitrin</td>
<td>extract of leaves</td>
<td>reported to inhibit monoamine oxidase but the dichloromethane fraction from areca nuts showed antidepressant activity in via MAO - A inhibition.</td>
<td>[160]</td>
</tr>
<tr>
<td>Areca catechu</td>
<td>Alkaloids such as arecaidine, arecoline and few other constituents.</td>
<td></td>
<td></td>
<td>[161-163]</td>
</tr>
<tr>
<td>Cimicifuga racemosa</td>
<td>Aqueous Ethanol extract (50 or 100 mg/kg)</td>
<td></td>
<td></td>
<td>[164]</td>
</tr>
<tr>
<td>Centella asiatica</td>
<td>triterpenes</td>
<td></td>
<td></td>
<td>[165]</td>
</tr>
<tr>
<td>H. canariensis</td>
<td>Naphthodianthrones (hypericin and pseudohypericin), Phloroglucinols (hyperforin and adhyperforin), flavinoids (flavonol glycoside, viz. rutin quercitrin, isorhamnetin, hyperin, hyperoside and aglycones, viz. kaempferol, luteolin, Myricetin, and quercitin), Xanthones, 1,3,6,7 - tetrahydroxynaphthoic acid, 50% aqueous ethanolic extract of Indian plant (100-200 mg/Kg p.o) roots in leaves and stems Methanol extract of the aerial parts</td>
<td></td>
<td>involved in inhibition of uptake of serotonin, Noradrenaline and Dopamine</td>
<td>[167-181]</td>
</tr>
<tr>
<td>Crocus sativus</td>
<td>hydro-alcoholic extract of Crocus sativus (stigma)</td>
<td></td>
<td></td>
<td>[182,183]</td>
</tr>
<tr>
<td>Bacopa monnieri</td>
<td>alkaloids (brahmine, herpestine)</td>
<td>methanolic standardized extract</td>
<td></td>
<td>[184]</td>
</tr>
<tr>
<td>Mangolia officinalis</td>
<td>Mangolol, and dihydroxydihydromangolol</td>
<td>aqueous extract of the bark</td>
<td></td>
<td>[185]</td>
</tr>
<tr>
<td>Curcuma longa</td>
<td>aqueous extracts</td>
<td></td>
<td>mediated through MAO-A inhibition</td>
<td>[186]</td>
</tr>
<tr>
<td>Mimosa pudica</td>
<td>aqueous extract from dried leaves</td>
<td></td>
<td></td>
<td>[187]</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>norepinephrine, and dopamine and serotonin</td>
<td></td>
<td></td>
<td>[188-190]</td>
</tr>
<tr>
<td>Ocimum sanctum</td>
<td>Ethanol extract of leaves, Methanol extract from roots</td>
<td></td>
<td>involving dopaminergic neurons</td>
<td>[191-196]</td>
</tr>
<tr>
<td>Rhazya stricta</td>
<td>alkaloids with β carboline nucleus (Akanumidine, rhazimine, and tetrahydroxycamine), flavinoids, namely isorhamnetin, 3 - (6-dimannosyl galactoside)-7-rhamnoside and 3- (6 - rhamnosyl galactoside) – 7 – rhamnoside</td>
<td>plant extract</td>
<td>inhibit both MAO-A and MAO-B</td>
<td>[197]</td>
</tr>
<tr>
<td>Rhizoma acori tatarinowii</td>
<td></td>
<td></td>
<td></td>
<td>[198]</td>
</tr>
<tr>
<td>Piper methysticum</td>
<td>pyrone</td>
<td>aqueous standardized extract of roots</td>
<td>inhibition of MAO-B mesolimbic dopaminergic neurons</td>
<td>[199,200]</td>
</tr>
<tr>
<td>Withania somnifera</td>
<td>glycowithanolides</td>
<td>Standardized extracts of roots</td>
<td></td>
<td>[201-203]</td>
</tr>
<tr>
<td>Siphocampylus verticillatus</td>
<td>Hydroalcoholic extract</td>
<td></td>
<td></td>
<td>[204]</td>
</tr>
<tr>
<td>Oenothera biennis</td>
<td>Evening primrose oil obtained from seeds</td>
<td></td>
<td></td>
<td>[205]</td>
</tr>
</tbody>
</table>
### Conclusion

Depression is known to adversely influence the physiological and psychological activities as it is directly associated with the functions of different regions of the human brain. The molecular and genetic bases of depression include polymorphs of different genes involved in stress and depression as shown in Table 1. The biochemical bases include alterations in the levels of various neurotransmitters and their metabolizing enzymes mentioned as above. The application of current antidepressants described as above help recover the patients suffering from depression but the longer use of these drugs lead to exert serious side effects. Keeping in view the urgent need of specific and target oriented antidepressants, there is immense possibility to explore certain phytochemicals which may prove to be relatively safer and more effective therapeutics to treat depression in future. There are a number of medicinal plants and formulations reported to exhibit antidepressant activity comparable to clinically effective synthetic antidepressants. However, except *H pertoratum*, more detailed clinical studies are required for the plants showing antidepressant activity in animal models.

### Acknowledgements

Vivek Kumar Gupta is grateful to the University Grant Commission, New Delhi for providing research scholarship for this work at the Department of Biochemistry, University of Allahabad, India.

### References

Citation: Sharma B, Gupta VK (2016) Modulations of Mammalian Brain Functions by Antidepressant Drugs: Role of Some Phytochemicals as Prospective Antidepressants. Evidence Based Medicine and Practice 1: 003. doi:10.4172/ebmp.1000003

Page 9 of 12


