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Natural therapeutics for the management of depression

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Abstract
Depression is a long-term mental illness that affects one's mood, emotions, actions, and physical health. The World Health Organization (WHO) estimates that 350 people worldwide suffer from this psychiatric illness. Major depression is estimated to have a lifetime prevalence of 14-17 percent and a one-year prevalence of 4-8 percent. Women have a 10-to-25 percent lifetime prevalence rate of major depressive disorders, while men have a 5-to-12 percent lifetime prevalence rate. There are many types of depression, ranging from moderate to severe, such as psychotic depression, in which patients experience hallucinations and delusions. There are many hypotheses about the pathogenesis of depression, the majority of which are focused on indirect marker measurements, post-mortem tests, and neuro-imaging techniques. Furthermore, over the years, a variety of treatment options for depression have been created. For treatment-resistant depression, multiple treatments such as pharmacotherapy, psychotherapy, and somatic therapy are commonly used. Since antiquity, medicinal plants have been used to cure diseases of the body and mind all over the world. Herbal medication has also proven to be a viable option for the treatment of mental illnesses such as anxiety, depression, and dementia, among many others. *Hypericum perforatum*, *Centella asiatica*, *Rhodiola rosea*, *Pfaffia paniculata*, *Rauwolfia serpentina*, *Rhododendron molle*, Schizandra chin, Thea sinensis, Uncaria tome, *Valeriana officinalis*, and *withania Somnifera* are the medicinal plants most commonly used to treat depression around the world.

Keywords: Depression, VTA (ventral tegmental region), NAc (nucleus accumbens), HVA (Homovenillic acid)

Introduction
In terms of its prevalence, as well as the suffering, dysfunction, morbidity, and economic burden it causes, depression is a major public health concern. Women are more likely than men to suffer from depression. The point prevalence of unipolar depressive episodes is estimated to be 1.9 percent for men and 3.2 percent for women in the Global Burden of Disease report, with a one-year prevalence of 5.8 percent for men and 9.5 percent for women [1]. If current demographic and epidemiological trends continue, the burden of depression is expected to rise to 5.7 percent of the total burden of disease by 2020, making it the second leading cause of disability-adjusted life years (DALYs), striking only ischemic heart disease. It has the potential to affect relationships as well as chronic health conditions such as asthma, diabetes, cancer, heart disease, and many others [2]. Feeling down and sad at different times in our lives is normal, but when it becomes miserable and hopeless, it needs to be examined; if left untreated, it can last for years and gets worse over time. Several medical conditions, such as vitamin deficiency and thyroid problems, can mimic depression symptoms [3]. The hallmark of major depressive disorder (MDD) is the occurrence of depressed mood (dysphoria) and loss of interest in previously pleasurable activities (anhedonia) for at least two weeks, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM- V). At least four of the following manifestations must accompany these symptoms: 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 [4]. Despite the fact that many drugs have been developed to treat depression, one of the difficulties in treating this disease is that a significant portion of patients who take antidepressants do not achieve full remission.

Some patients develop treatment-resistant depression, a condition in which they do not respond to available medications or other therapeutic approaches [5].

Pathogenesis of Depression

There are numerous theories about the pathogenesis of depression, the majority of which are based on indirect marker measurements, post-mortem studies, and neuro-imaging techniques. Following the serendipitous discovery of imipramine and iproniazid as antidepressants, depression pharmacotherapy and an explanation for the underlying pathology focused on the brain monoamine neurotransmitters level for centuries [6].

A) Depression's Neural circuitry

Various structural and functional studies have found abnormalities in the areas of the brain responsible for mood regulation, reward response, and executive functions. Reduced 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, have been reported in post-mortem and neuroimaging studies. Hippocampal dysfunction, which is thought to have an inhibitory effect on the hypothalamic-pituitary-adrenal (HPA) axis, could be to blame for the hypercortisolemia seen in depression [7-8]. The nucleus accumbens (NAc) and the ventral tegmental region (VTA), which make up the mesolimbic dopamine system, are both thought to play a role in the pathogenesis of depression. The reward response to pleasurable stimuli such as food, sex, and even drugs is mediated by these brain regions. As a result, a distinct loss of stimulation in depressed patients may be explained by a deficiency of this brain reward circuit. Other research has shown a reduction in Locus coeruleus (LC) neuron density in suicidal and suicide patients as compared to controls [9].

B) Stress response circuits

Chronic stress and hyperactivity of the HPA axis (resulting in chronic hypercortisolemia) have been suggested to play a significant role in the occurrence of depression and even recurrence after full remission. Patients with high levels of corticosteroids have been shown to have structural brain defects. The amygdala, a brain structure involved in controlling emotional reactivity and, to a lesser extent, stress response, is one of the brain structures affected [10]. The hippocampus, an area of the brain that is thought to exert an inhibitory signal to the HPA axis, has also been shown to shrink in size as a result of chronic corticosteroid administration [11]. There is also a gap in our knowledge of how behavioural stress leads to depression. Chronic stress, on the other hand, has been shown to alter the expression of genes that regulate antioxidant systems including superoxide dismutases (SODs), catalase, glutathione peroxidase, glutathione reductase, and NADPH oxidase. Furthermore, animal studies have discovered that glucocorticoids cause an increase in reactive oxygen species (ROS) levels both *in vitro* and in the brains of animals, as well as down-regulation of various antioxidant enzymes and depression-like conduct [12].

C) Environmental interaction and genetic vulnerability

There is now a convincing argument that for depression to emerge, a complex gene-environmental interaction that alters an individual's response to stressful life circumstances is required. While no single gene polymorphism appears to be responsible for depression, it has been proposed that genetic factors increase a person's susceptibility to stressful environmental factors, making them more susceptible to depression [13-14]. Allelic variation in the promoter region of the gene encoding the serotonin transporter is a genetic polymorphism that has gotten a lot of attention in recent years (5- HTT). A functional polymorphism in the promoter region of the 5-HTTLPR gene results in a long (L)/short(S) variant in the promoter region upstream of the transcription starting site. The low-activity short allele of 5-HTT has been shown to place carriers at a higher risk of developing depression in response to stressful life events. This allele has also been linked to less effective antidepressant pharmacological and non-pharmacological therapies [15-16]. Tryptophan hydroxylase (TPH), the rate-limiting enzyme in serotonin biosynthesis, is encoded by two genes, Tphl and Tph2, and has been linked to the pathogenesis of depressive disorders and suicide. Single nucleotide polymorphisms (SNPs) in the Tph2 gene have been linked to an increased incidence of MDD and attempted suicide. In addition, the Tph l gene, which is primarily expressed in the pineal gland, is thought to affect suicidal risk by interfering with the production of melatonin, a hormone that regulates circadian rhythm and thus increases suicidal risk [17-18]. A functional polymorphism in the BDNF gene has been reported, resulting in a valine to methionine substitution at codon 66 (Val66Met) in the pro-BDNF region, which has a negative impact on intracellular trafficking and activity-dependent secretion, as well as influencing hippocampal function, episodic memory, and brain morphology. Healthy people who have the BDNF Met form have lower emotional control and a smaller hippocampus capacity. Studies also indicate that polymorphisms in the genes encoding BDNF and 5-HTT interact in a complex way to produce a depressed phenotype [19].

D) The biogenic monoamine theory

After the serendipitous discovery of the first antidepressant medications, which were originally formulated for other medical conditions, the monoamine theory of depression was born. These clinical findings have made a significant contribution to our understanding of the pathophysiological changes that occur in depressed people's brains. The drugs were designed to increase the amount of monoamine neurotransmitters in the brain by inhibiting either the monoamine degrading enzyme monoamine oxidase inhibitor (MAOI) or the reuptake of neurotransmitters through presynaptic neurons [20].

i) The serotonin hypothesis

Serotonin is a monoamine neurotransmitter that has a wide range of distribution in the central nervous system. It plays a role in physiologic functions including pain perception, appetite control, aggression, and mood. Mood and anxiety disorders have been linked to serotonergic system dysfunction. The fact that the first antidepressant medications succeeded by reviving the brain's reduced monoamine function is the reason for this theory. Later, it was discovered that SSRIs alone is successful in treating depressive symptoms. This fact added to the evidence that 5-HT plays a role in the disease's pathogenesis [21-22]. A lower level of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of 5-

HT in the cerebrospinal fluid (CSF), has been linked to aggressive activity as well as increased suicidal intent and impulsivity in a subset of depressed patients. The plasma level of the 5-HT amino acid precursor (tryptophan) decreased, and depletion of this amino acid may trigger depressive symptoms in patients who are prone to depression. Furthermore, positron emission tomography (PET) imaging tests on depressed patients have shown a decrease in the density of the 5-HT1A receptor subtype in various brain regions. The availability of 5-HTT in the midbrain and brainstem is also reduced. However, whether serotonergic dysfunction is an etiologic factor or increases vulnerability to depression is a source of tension [23-24].

ii) **The catecholamine hypothesis**

The catecholamine theory of depression was proposed in the 1960s after it was discovered that reserpine, an antihypertensive drug, caused depression by depleting central and peripheral amine storage in the nervous system. However, there has been no clear evidence of a change in the levels of NE metabolites in the CSF of depressed people. In subsequent years, the "supersensitivity hypothesis," which ties depression to supersensitive presynaptic 2-R, was proposed, which is confirmed by increased density of these receptor types in post mortem studies, resulting in impaired NE operation [25-26]. Furthermore, some depressive symptoms, such as anhedonia and psychomotor retardation, are best explained by a disruption in the brain's DA processes. The substantia nigra-basal ganglia motor system, as well as reward circuitry involving the NAc and VTA, are among these systems. In the NAc, there is a decrease in DA activity, which leads to the failure to feel pleasure, which is one of the hallmarks of depression. In depressed patients, the concentration of the dopamine metabolite homovanillic acid (HVA) in CSF is also stated to be lower [27-28].

Current treatment

The treatment is called Stanford Accelerated Intelligent Neuromodulation Therapy, or SAINT. It is a form of transcranial magnetic stimulation, which is approved by the Food and Drug Administration for treatment of depression [29]. To treat patients with extreme depression, Stanford Medicine researchers used high doses of magnetic stimulation administered on an accelerated schedule and tailored to person neurocircuitry. In a small study conducted by researchers at Stanford University School of Medicine, a new form of magnetic brain stimulation quickly relieved symptoms of extreme depression in 90% of participants [30]. The researchers are currently performing a bigger, double-blind study in which half of the participants will be given a placebo. The researchers are hopeful that the second trial will be just as effective in treating people whose symptoms haven't responded to medicine, talk therapy, or other types of electromagnetic stimulation. Stanford Accelerated Intelligent Neuromodulation Therapy, or SAINT, is the name of the procedure. It is a form of transcranial magnetic stimulation that has been approved by the FDA for the treatment of depression [31].

Following that, 19 of them scored in the nondepressed category. Despite the fact that all of the participants had suicidal thoughts prior to the therapy, none of them said they had suicidal thoughts afterward. Medication, FDA-approved transcranial magnetic stimulation, or electroconvulsive therapy had previously tried to prepare all 21 patients. According to the report, the only side effects of the new therapy were fatigue and some pain during treatment. The findings were published in the American Journal of Psychiatry [32].

Calming the brain chatter

Electric currents from a magnetic coil mounted on the scalp excite a brain region linked to depression in transcranial magnetic stimulation. The FDA has approved the procedure, which entails six weeks of once-daily sessions. Just about half of those who receive this medication recover, and just about a third of those who receive it experience depression remission [33]. Some changes to transcranial magnetic stimulation, according to Stanford researchers, may increase its effectiveness. According to studies, a higher dose of 1,800 pulses per session, rather than 600, would be more efficient. The researchers were cautiously optimistic about the treatment's safety since that dosage of stimulation had previously been used safely in other types of brain stimulation for Other research indicated that speeding up the therapy could make patients feel better faster [34]. Participants in the SAINT study received ten 10-minute treatments a day, with 50-minute breaks in between. Lehman's mood score showed she was no longer depressed after only one day of therapy; other participants needed up to five days [35].

The study's lead author, postdoctoral scholar Eleanor Cole, PhD, said, "The fewer treatment-resistant participants are, the longer the treatment lasts."isorders like Parkinson's disease [36].

Strengthening a weak connection

The researchers also hypothesised that more specifically targeting the stimulus would increase the treatment's efficacy. Transcranial magnetic stimulation targets the dorsolateral prefrontal cortex, which is found in the majority of people. This area controls executive functions such as memory selection and inhibition of inappropriate responses [37]. The researchers used magnetic resonance imaging of brain activity to identify the dorsolateral prefrontal cortex, as well as a specific subregion within it, for SAINT. They identified the subregion of each participant that is linked to the subgenual cingulate, a part of the brain that is overactive in depressed people. Sixty percent of the participants were still depressed one month after the therapy. The length of the antidepressant effects is being investigated in follow-up research. SAINT's effectiveness in other conditions, such as obsessive-compulsive disorder, addiction, and autism spectrum disorders, will be investigated by the researchers [38].

Limitations of current treatment of depression

Modest efficacy

SSRIs are currently the most commonly used first-line antidepressants, and a recent meta-analysis of primary care trials concluded that SSRIs are more effective than placebo. However, there is no proof that they are more effective than TCAs as a group. In primary care, a systematic study of comparisons of SSRIs and TCAs revealed a small yet non-significant efficacy gap in favour of TCAs. A wider study of 315 randomised trials found no differences in effectiveness between newer and older agents, or between different newer

agents [39]. Variations in research populations, outcome measures used and whether they were continuous or categorical, and drug doses compared complicate interpretation of observed efficacy discrepancies between individual drugs based on single studies or meta-analyses. Nonetheless, some drugs, including clomipramine, escitalopram, and venlafaxine, have reasonable proof of superior efficacy [40].

Clomipramine was found to be more effective than citalopram, paroxetine, and moclobemide by the Antidepressant Community. In patients with endogenous depression, the difference in the number of complete responders was substantial as compared to citalopram, but the findings of both treatments were identical in those with non-endogenous depression. Venlafaxine, a dual-action serotonin-norepinephrine reuptake inhibitor, has shown superior efficacy in hospitalised patients with major depression and melancholia when compared to fluoxetine, according to several subsequent meta-analyses [41]. The evidence for venlafaxine's superiority comes primarily from its use at higher doses (150 mg), when its effect on nor epinephrine reuptake becomes more pronounced. In two recent trials, escitalopram outperformed citalopram in patients with extreme major depressive disorder. According to meta-analyses, escitalopram is more effective than citalopram and other antidepressants. Escitalopram tends to have a greater relative benefit in patients with more severe depression [42].

Suicidality

A field of current interest and debate is the effectiveness of antidepressants in preventing suicide. Data from observational studies have usually been reassuring. Among a groupof 406 patients with mood disorders followed for up to approximately 40 years, drug treatment was associated with a significant reduction in suicide, despite more severe illness among treated patients [43]. Suicide rates in Sweden in the early 1990s were found to be markedly lower in treated compared with untreated depressives, and increases in sales and prescribing rates of SSRIs are associated with reductions in suicide rates,at least in adults. Many variables, however, can affect population suicide rates, and in some nations, the decline in suicide rates occurred before the increase in antidepressant sales [44]. A new study of suicidal behaviour in over 65000 depressed people found that the risk of a severe suicide attempt (resulting in hospitalisation) was higher in the month before beginning antidepressant treatment and gradually decreased after that. The authors note that while this trend is consistent with a decrease in risk after starting treatment, the fact that a suicide attempt may cause treatment initiation may also be a factorFinally, antidepressant use can affect the risk of attempted suicide and completed suicide in different ways [45]. A cohort analysis of over 15000 patients hospitalised for suicide attempts in Finland showed that current antidepressant use was associated with a significantly increased risk of attempted suicide but a significantly lower risk of completed suicide as compared to no current antidepressant use. In terms of the risks associated with various drug types, studies across counties in the United States found that prescribing SSRIs and other new-generation antidepressants was linked to lower suicide rates, whereas prescribing TCAs was linked to a higher suicide rate [46]. In comparison, a recent nested case–control analysis based on the UK General Practice Research Database found no evidence that SSRIs or TCAs increased the risk of suicide or non-fatal self-harm in adults. It's likely that a high incidence of TCA prescribing is a sign of a community with poor mental health services and insufficient depression treatment, leading to a higher risk of suicide. Comparisons between drug groups are further complicated by two additional factors [47]. There is evidence that antidepressants are administered differently to people who are at risk of suicide, and there is no question that SSRIs are less dangerous in overdose than TCAs. While randomised trials escape the problems of confounding and prejudice that plague observational studies, the low incidence of suicide even among depressed people means that a trial involving about 2 million people will be needed to reliably detect a significant impact of treatment on danger. Antidepressant therapy has not been shown to raise or decrease suicide rates in pooled studies of randomised trials [48]. Based on patient-years of exposure, suicide rates for SSRIs and other antidepressants were 0.59 percent for SSRIs and 0.76 percent for other antidepressants, which were not substantially different from placebo, according to a review of FDA data involving 48277 depressed patients and 77 completed suicides (0.45 percent). While the 95 percent critical interval was very wide, data from the UK Medicine and Healthcare Products Regulatory Agency for 342 placebo-controlled clinical trials of SSRIs produced just 16 suicides, with an odds ratio of 0.85 for SSRIs compared to placebo (0.20 to 3.40). This study looked at non-fatal self-harm episodes from 382 studies and found that adults taking SSRIs had a higher incidence than those taking placebo (odds ratio 1.57). The 95 percent critical period (0.99 to2.55) was consistent with a risk doubling, but there was no evidence of risk reduction [49]. Overall, there is no hard evidence that current antidepressant medications raise the risk of suicide in adults. Nonetheless, considering their extensive use in recent years, it's disappointing that more convincing proof of gain in significantly lowering suicide risk is lacking [50].

Tolerability

TCAs have a variety of pharmacological effects and are linked to a variety of side effects. With a more limited range of acts, SSRIs appear to have less side effects. Blurred vision, constipation, dizziness, dry mouth, tremors, and urinary discomfort were significantly more common with TCAs than with SSRIs, according to a review of evidence from 315 mostly short-term trials, while nausea, headache, diarrhoea, and insomnia were significantly more common with SSRIs [51]. Dual-action antidepressants, such as SNRIs, can have a broader variety of side effects than SSRIs, but they are usually tolerated better than TCAs. Adverse events of at least moderate severity are most common early in the course of treatment with SSRIs and decrease over time, particularly in men. In a meta-analysis of direct comparisons in primary care between TCAs and SSRIs, the relative risk of dropout due to a drug-related adverse event with SSRI was 0.75 times higher than with TCA (95 percent CI 0.60 to 0.88) [52]. The disparity was less pronounced in trials comparing the two drug groups to placebo; the relative risk of dropout due to adverse effect was 2.35 (95 percent CI 1.59 to 3.46) for TCAs and 2.01 (95 percent CI 1.1 to 3.7) for SSRIs. Weight gain, sexual dysfunction, sleep disturbances, exhaustion, and cognitive decline are among

the long-term side effects of antidepressant therapy that have received less attention [53].

Natural Products for the treatment of depression

Role of alkaloids

Various plant alkaloids have been shown to have antidepressant properties in the literature (Table-1). When studied on a 5-HT device in the rat hippocampus, a Brazilian group of researchers isolated strictosidinic acid from Psychotria myriantha Mull, which had an antidepressant-like impact. In the Forced swim test, berberine administration reduced immobility and improved climbing activity. There was no impact on swimming time, but there was an improvement in open-arm exploration in the elevated plus maze test, indicating that the antidepressant-like activity was confirmed [54]. 1,2-dimethoxy-5,6,6a,7-tetrahydro-4H-dibenzoquinoline-3,8,9,10-tetraol, anonaine, liriodenine, and nornuciferine were among the alkaloids isolated from Annona cherimolia. Repeated treatment with this plant developed an antidepressant-like effect in mice, according to the findings. In the mouse forced swim test, the -carboline alkaloids harmane, norharmane, and harmine decreased immobility time in a dose-dependent manner, producing an antidepressant-like effect. Rhazya stricta was used to isolate Akuammidine, rhaziminine, and tetrahydrosecamine by a research team [55]. In laboratory animals, acute administration of the lyophilized extract of R. stricta produced a major antidepressant-like effect. Idayu and his Malaysian colleagues discovered mitagynine as an active component of Mitagyna spicosa in 2011. In both the forced swim test and the tail suspension test, mitagynine i.p injection significantly decreased the immobility period of mice without having any effect on locomotor function [56]. Mauritine A, an active compound found in Ziziphus apetala, showed good activity against 11-hydroxysteroid dehydrogenase inhibition *in vitro*, according to a team from the Republic of China. In an animal model of depression, the diterpene alkaloids (Napelline, songorine, hypaconitine, and mesaconitine) isolated from Aconitum baicalens exhibited an antidepressant-like effect. Punaravine, an alkaloid found in Boerhaavia diffusa Linn, was isolated by Dhingra and Valecha [57]. In different models, it showed important antidepressant activity in both unstressed and stressed mice. Purified Evodamine from Evodia fructus was found to increase immobility time while also reversing sucrose preference, number of crossings, 5-HT, and Na levels. Mesembrine, contained in Sceletium tortuosum, was found to have antidepressant properties in animal experiments by a team from the United States. Piperine, a major alkaloid isolated from Piper nigrum, was evaluated by Wattanathorn [58]. It has been shown to have antidepressant properties in mice that have been exposed to both chronic and acute stress. It resulted in a major shift in immobility as well as swimming times. From Piper laetispicum, a team from the China School of Pharmacy isolated Leatispicine, an amide alkaloid. It induced a major dose-dependent decrease in mobility in the forced swim test at different test doses, indicating that it had antidepressant efficacy [59]. Propine, which was obtained from the Chinese plant Dactylicapnos scandens Hutch, had an antidepressant effect in mice, according to Xu and colleagues. It decreased immobility time in the tail suspension test in a dose-dependent manner, suggesting that it may be useful in the treatment of moderate depression. In addition, pramipexole, a non-ergoline alkaloid, demonstrated substantial clinical effectiveness in bipolar and unipolar depressive patients in a double-blind, placebo-controlled trial [60].

Mechanism of Anti depressant in plant alkaloids

Strictosidinic acid's antidepressant effect was most likely due to its inhibition of monoamine oxidase activity. An increase in monoaminergic turnover induced an antidepressant-like effect in 1,2-dimethoxy-5,6,6a,7-tetrahydro-4H-dibenzoquinoline-3,8,9,10-tetraol, anonaine, liriodenine, and nornuciferine. Berberine, an isoquinoline alkaloid found in barberries, has been shown to have antidepressant properties through serotonergic, noradrenergic, and dopaminergic intervention [61]. By interacting with MAO-A and other cell-surface receptors, including serotonin receptor 2A, the -carboline alkaloids (harmane, norharmane, and harmine) induced antidepressant-like effects. A biphasic effect on the MAOA inhibitory portion of tribulin was observed when akuammidine, rhaziminine, and tetrahydrosecamine were used as potential mechanisms. Mitagynine had an antidepressant-like effect by lowering corticosterone levels [62]. *In vitro*, mauritine A has a powerful inhibitory effect on 11-hydroxysteroid dehydrogenase, which may be the mechanism for its antidepressant effect. In an animal model of depression, the diterpene alkaloids of Aconitum baicalense enhanced serotonergic system function. Punaravin E appears to work by inhibiting MAOA activity in the brain and also has antidepressant properties, likely due to a reduction in plasma corticosterone levels [63]. The modulating effects of Evodamine on monoamine transmitters and BDNF-TrkB signalling in the hippocampus may be related to the underlying mechanism. Mesembrine, an alkaloid, works as an antidepressant by blocking 5HT reuptake. Piperine has been shown to increase serotonin levels in the cerebral cortex and limbic regions, resulting in anti-depressive effects. However, further research into the precise underlying mechanism is still required [64]. The central nervous system monoaminergic neurotransmitters is thought to be the target of leatispicine's action. *In vitro* assays have shown that protopine inhibits both serotonin and noradrenaline transporters [65].

Role of Flavonoids

Hesperidin, a flavanone glycoside found primarily in citrus fruits, has been linked to beneficial therapeutic properties such as antidiabetic, antioxidant, neuroprotective, and anticancer. Hesperidin's antidepressant activity in streptozotocin-induced diabetic rats. Hesperidin's effects are mediated, at least in part, by its modulatory effect on hyperglycemia, antioxidant and anti-inflammatory activities, changes in BDNF levels, and activation of the brain's monoaminergic system, according to the findings [66]. In addition, chronic hesperidin administration resulted in an improvement in hippocampal BDNF levels. The antidepressant effect of hesperidin, according to these researchers, is mediated by inhibition of the L-arginine-NO-cGMP pathway and an increase in BDNF levels in the hippocampus [67]. In mice subject to chronic mild stress, hesperidin has an antidepressant-like mechanism (CMS). The findings revealed that hesperidin would help to alleviate sucrose preference loss and reverse the increased immobility period caused by CMS. All of these findings support

hesperidin's antidepressant activity and indicate that the extracellular signal-regulated kinase (ERK-) BDNF signalling pathway is involved in this flavanone's antidepressant-like activity [68].

Chrysin (2), a natural flavonoid predominant in bee propolis, honey, and several plants, possesses multiple biological activities such as anti-inflammatory, antineoplastic, hypolipidemic, and antioxidant. In addition, revealed the antidepressant effect of chrysin in mice subjected to chronic unpredictable mild stress [69]. The authors proposed that upregulation of BDNF levels in the hippocampus and prefrontal cortex of stressed mice may be associated with the antidepressant effects of chrysin. In another study done by the same research group members [70]. They discovered that chrysin therapy reduced depressive-like behaviour and hippocampal changes in olfactory bulbectomized mice, indicating that BDNF plays a key role in this flavonoid's antidepressant impact. In addition, the neurochemical parameters associated with chrysin's antidepressant property in mice exposed to unpredictably persistent stress were investigated [71]. The authors proposed a link between chrysin's antidepressant-like action and the production of proinflammatory cytokines, 5-hydroxytryptamine metabolism, the kynurenine pathway, and caspase activity [72].

Naringenin (3), a dietary flavonoid found in citrus fruit peels, has a number of biological effects, including acting as a cognitive enhancer, inhibiting monoamine oxidase activity, and providing neuroprotection. Similarly, naringenin was discovered to have antidepressant properties. The researchers concluded that naringenin therapy suppresses neuroendocrine signalling and stimulates monoamines, resulting in BDNF upregulation in the hippocampus of mice [73].

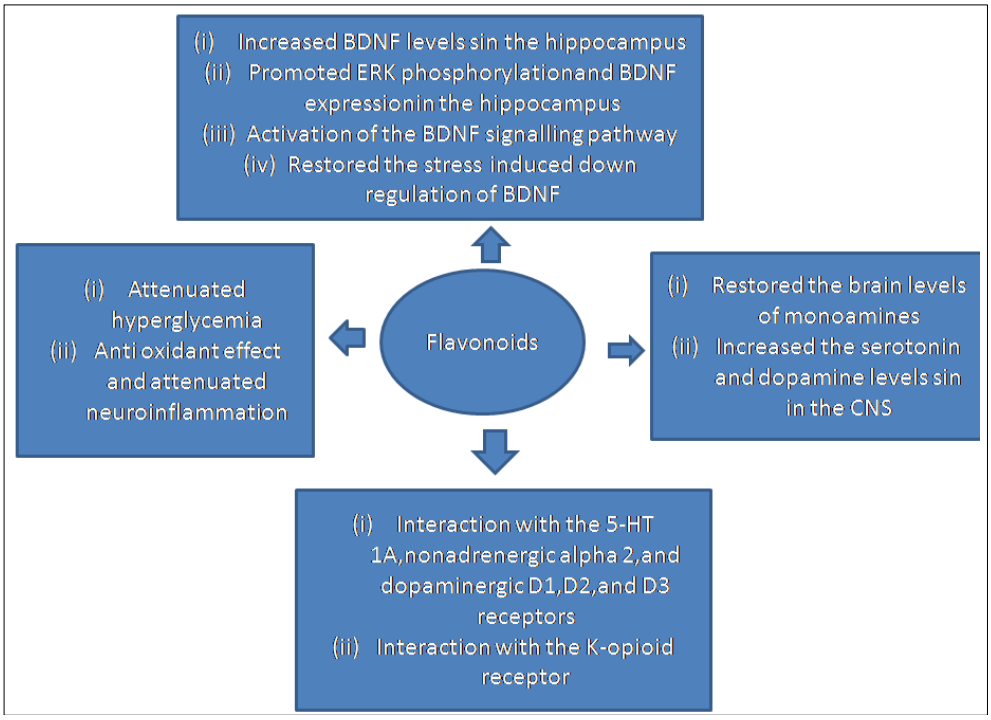

Fig 1: Role of Flavonoids

Astilbin (4), a flavonoid heteroside found in Smilax or *Hypericum perforatum* L. plants, has a variety of pharmacological effects including antioxidant, free radical scavenging, and anti-inflammatory properties. They hypothesised that astilbin's antidepressant effects are mediated by upregulation of the BDNF signal pathway and monoaminergic neurotransmitter discharge in the mouse cortex [74].

Icariin (5) is a significant bioactive compound found in the traditional Chinese medicinal herb Herba Epimedii (Epimedium brevicornum Maxim), which has been used for centuries to treat a variety of ailments, including depression. Icarin, one of 19 metabolites derived from icariin, has been shown to have neuroprotective properties. Icaritin is a novel antidepressant that partially reversed the effects of social defeat on glucocorticoid sensitivity and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Normalization of glucocorticoid receptor activity and increases in BDNF expression are at least partly responsible for these effects [75]. In addition, icariin has been linked to the control of hippocampal neuroinflammation and has an antidepressant effect in an unstable chronic mild stress model of depression in rats. The results of icariin treatment in a model of depression in rats caused by unpredictable chronic mild stress were investigated in another study. The findings point to icariin's therapeutic effectiveness as a potential antidepressant. Furthermore, this flavonoid heteroside's antidepressant function is mediated by various targets in the hippocampus and prefrontal cortex [76].

Hyperoside (7) is a flavonoid isolated from the leaves of Apocynum venetum L. Within the PC12 cell line, the hyperoside has antidepressant effects via cytoprotective action linked to the elevation of BDNF and CREB expression via the AC-cAMP-CREB signal pathway. Furthermore, this flavonoid heteroside, derived from the crude extract of Hypericum caprifoliatum Cham. & Schltdl. (Guttiferae), had a depressant effect on the central nervous system (CNS) and either an antidepressant effect in rodents, both of which were mediated by D2-DA receptor activation [77].

Baicalein (8) One of the most active flavonoids found in the dry roots of Scutellaria baicalensis Georgi is baicalein.

Baicalein has been stated to be able to cross the BBB. Baicalein has also been shown to be a superior free radical scavenger and xanthine oxidase inhibitor in different studies. This flavone was found to have antidepressant properties. In the hippocampus of chronic mild stress model rats, baicalein also reversed the reduction of ERK phosphorylation and the degree of BDNF expression. These findings indicate that baicalein has an antidepressant-like effect, which is at least partially mediated by ERK-mediated neurotrophic activity in the hippocampal nucleus. Furthermore, baicalein inhibited cyclooxygenase-2 in the rat brain, which resulted in a reduction of prostaglandin E2 levels in the brain, preventing chronic mild stress-induced depressivelike actions [78].

The polymethoxyflavone 3, 5, 6, 7, 8, 3′, 4′-Heptamethoxyflavone (9) is present in a variety of citrus fruits. Anti-inflammatory, neuroprotective, and immunomodulatory properties are among the biological activities of this polymethoxyflavone. According to the authors of a study conducted by Sathese, the 3, 5, 6, 7, 8, 3′, 4′-heptamethoxyflavone has antidepressant activity by inducing the expression of BDNF. This flavone enhanced depression-like behaviour caused by corticosterone, as well as BDNF expression, neurogenesis, and neuroplasticity in the hippocampus [79].

Conclusion

Depression is a widespread condition that ranks third in terms of major causes of impairment after cardiac and respiratory illnesses.Sleep disorder is the most common symptom of depression that affects people's ability to function during the day. Sleep problems are frequently a major motivator for a depressed patient to seek medical treatment. As new types of medications, such as SSRIs, have been launched, the use of antidepressants has risen dramatically. However, the effectiveness and tolerability benefits of newer medications are modest, and there are still drawbacks associated with their use in many key areas.

Several alkaloids have been tested in clinical trials and have shown to be effective in a variety of therapeutic groups. While these alkaloids have been shown to have antidepressant effects in animal studies, clinical evidence is still lacking. Finally, the scientific evidence gathered in our analysis showed that plant-based alkaloids can be used as leads for the development of antidepressant drugs.

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global Burden of Disease and Risk Factors. Washington: The World Bank; c2006.
2. Legg TJ. Depression Overview. Healthline Newsletter; c2016. Available from: [insert URL or additional details].
3. Parekh R. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Fifth edition 2013; c2017.
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Publishing; c2013.
5. Al-Harbi K. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Preference and Adherence. 2012;6:369-388.
6. Grønli J. Chronic mild stress: an animal model of depression. University of Bergen, Norway; c2006.
7. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008;455:894-902.
8. Nestler EJ, Carlezon WA Jr. The mesolimbic dopamine reward circuit in depression. Biological Psychiatry. 2006;59:1151-1159.
9. Ressler KJ, Nemeroff CB. Role of norepinephrine in the pathophysiology and treatment of mood disorders. Biological Psychiatry. 1999;46:1219-1233.
10. Bouhuys L, Bos H, Geerts E, Van S, Ormel J. The association between levels of cortisol secretion and fear perception in patients with remitted depression predicts recurrence. Journal of Nervous and Mental Disease. 2006;194:478-484.
11. Brown S, Woolston J, Frol B. Amygdala volume in patients receiving chronic corticosteroid therapy. Biological Psychiatry. 2008;63:705-709.
12. Lee S, Jeong J, Kwak Y, Park SK. Depression research: where are we now? Molecular Brain. 2010;3:8.
13. Swaab DF, Bao AM, Lucassen PJ. The stress system in the human brain in depression and neurodegeneration. Ageing Research Reviews. 2005;4:141-194.
14. Bocchio-Chiavetto L, Miniussi C, Zanardini R, Gazzoli A, Bignotti S, *et al*. 5-HTTLPR and BDNF Val66Met polymorphisms and response to rTMS treatment in drug-resistant depression. Neuroscience Letters. 2008;437:130-134.
15. Karg K, Burmeister M, Shedden K, Sen S. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited. Evidence of genetic moderation. Archives of General Psychiatry. 2011;68:444-454.
16. Stefulj J, Kubat M, Alija M, Jernej B. TPH gene polymorphism and aging: Indication of combined effect on the predisposition to violent suicide. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2006;141:139-141.
17. Zupanc T, Pregelj P, Paska A. Tryptophan hydroxylase 2 (TPH 2) single nucleotide polymorphisms, suicide, and alcohol-related suicide. Psychiatria Danubina. 2013;25:332-336.
18. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008;455:894-902.
19. Nutt D. The role of dopamine and norepinephrine in depression and antidepressant treatment. Journal of Clinical Psychiatry. 2006;6:3-8.
20. Cowen PJ. Serotonin and depression: pathophysiological mechanism or marketing myth? Trends in Pharmacological Sciences. 2008;29:433-436.
21. Saldanha D, Kumar N, Ryali V, Srivastava K, Pawar AA. Serum serotonin abnormality in depression. Medical Journal Armed Forces India. 2009;65:108-112.
22. Drevets W, Thase M, Mathis C. Serotonin-1A receptor imaging in recurrent depression: Replication and literature review. Nuclear Medicine and Biology. 2007;34:865-877.
23. Jans L, Riedel W, Markus C, Blokland A. Serotonergic vulnerability and depression: assumptions, experimental evidence and implications. Molecular Psychiatry. 2007;12:522-543.
24. Ressler KJ, Nemeroff CB. Role of norepinephrine in the pathophysiology and treatment of mood disorders. Biological Psychiatry. 1999;46:1219-1233.

25. Nutt D. The role of dopamine and norepinephrine in depression and antidepressant treatment. Journal of Clinical Psychiatry. 2006;6:3-8.
26. Brunswick D, Amsterdam J, Mozley D, Newberg A. Greater availability of brain dopamine transporters in major depression shown by 99mTcTRODAT-1 SPECT Imaging. American Journal of Psychiatry. 2003;160:1836-1841. DOI: 10.1176/appi.ajp.160.10.1836.
27. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neuroscience & Biobehavioral Reviews. 2011;35:537-555. DOI: 10.1016/j.neubiorev.2010.06.006.
28. Zupanc T, Pregelj P, Paska A. Tryptophan hydroxylase 2 (TPH 2) single nucleotide Polymorphisms, suicide, and alcohol-related suicide. Psychiatria Danubina. 2013;25:332-336.
29. Nutt D. The role of dopamine and norepinephrine in depression and antidepressant treatment. Journal of Clinical Psychiatry. 2006;6:3-8.
30. Cowen PJ. Serotonin and depression: pathophysiological mechanism or marketing myth? Trends in Pharmacological Sciences. 2008;29:433-436.
31. Saldanha D, Kumar N, Ryali V, Srivastava K, Pawar AA. Serum serotonin abnormality in depression. Medical Journal Armed Forces India. 2009;65:108-112.
32. Drevets W, Thase M, Mathis C. Serotonin-1A receptor imaging in recurrent depression: Replication and literature review. Nuclear Medicine and Biology. 2007;34:865-877.
33. Jans L, Riedel W, Markus C, Blokland A. Serotonergic vulnerability and depression: assumptions, experimental evidence and implications. Molecular Psychiatry. 2007;12:522-543.
34. Brunswick D, Amsterdam J, Mozley D, Newberg A. Greater availability of brain dopamine transporters in major depression shown by 99mTcTRODAT-1 SPECT Imaging. American Journal of Psychiatry. 2003;160:1836-1841. DOI: 10.1176/appi.ajp.160.10.1836.
35. Martinot M, Bragulat V, Artiges E, Dollé F, Hinnen F, *et al*. Decreased presynaptic dopamine function in the left caudate of depressed patients with affective flattening and psychomotor retardation. American Journal of Psychiatry. 2001;158:314-316.
36. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neuroscience & Biobehavioral Reviews. 2011;35:537-555. DOI: 10.1016/j.neubiorev.2010.06.006.
37. Dolati K, Rakhshandeh H, Shafei M. Evaluation of antidepressant effect of ethanolic extract of Rosa damascene using forced swimming test. Avicenna Journal of Phytomedicine. 2011;2:46-51.
38. Vogelzangs N, Duivis H, Beekman A, Kluft C, Neuteboom J, *et al*. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. Translational Psychiatry. 2012;2:e79. DOI: 10.1038/tp.2012.8.
39. Audet MC, Anisman H. Interplay between pro-inflammatory cytokines and growth factors in depressive illnesses. Frontiers in Cellular Neuroscience. 2013;7:68. DOI: 10.3389/fncel.2013.00068.
40. Maes M, Fisar Z, Medina M, Scapagnini G, Nowak G, *et al*. New drug targets in depression: inflammatory, cell-mediated immune, oxidative and nitrosative stress, mitochondrial, antioxidant, and neuroprogressive pathways and new drug Candidates-Nrf2 activators and GSK-3 inhibitors. Inflammopharmacology. 2012;20:127-150. DOI: 10.1007/s10787-011-0111-7.
41. Groves JO. Is it time to reassess the BDNF hypothesis of depression? Molecular Psychiatry. 2007;12:1079-1088. DOI:10.1038/sj.mp.4002075.
42. Sirianni RW, Olausson P, Chiu AS, Taylor JR, Saltzman WM. The behavioral and biochemical effects of BDNF-containing polymers implanted in the hippocampus of rats. Brain Research. 2010;1321:40-50. DOI:10.1016/j.brainres.2009.11.057.
43. Angelucci F, Brene` S, Mathe A. BDNF in schizophrenia, depression and corresponding animal models. Molecular Psychiatry. 2005;10:345-352. DOI:10.1038/sj.mp.4001574.
44. Heldt S, Stanek L, Chhatwal J, Ressler K. Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. Molecular Psychiatry. 2007;12:656-670. DOI: 10.1038/sj.mp.4001997.
45. Molendijk M, Bus B, Spinhoven P, Penninx B, Kenis G, *et al*. Serum levels of brain-derived neurotrophic factor in major depressive disorder: state–trait issues, clinical features and pharmacological treatment. Molecular Psychiatry. 2011;16:1088-1095. DOI:10.1038/mp.2010.98.
46. Huuhka K. Electroconvulsive therapy. Association of genetic polymorphisms with treatment-resistant depression and treatment response. Tampere University Hospital, Department of Psychiatry and Centre for Laboratory Medicine and Department of Clinical Chemistry, Finland; c2009.
47. Thakker-Varia S, Alder J. Neuropeptides in depression: role of VGF. Behavioural Brain Research. 2009;197:262-278. DOI:10.1016/j.bbr.2008.07.038.
48. Brain S, Cox H. Neuropeptides and their receptors: Innovative science providing novel therapeutic targets. British Journal of Pharmacology. 2006;147:202-211. DOI:10.1038/sj.bjp.0706427.
49. Herpfer I, Lieb K. Substance P receptor antagonists in psychiatry: rationale for development and therapeutic potential. CNS Drugs. 2005;19:275-293. DOI:10.2165/00023210-200519040-00003.
50. Holtzheimer PE, Nemeroff CB. Novel targets for antidepressant therapies. Current Psychiatry Reports. 2008;10:465-473.
51. Pedrazuela A, Venero C, Autric R, Lamo I, Verdugo J, *et al*. Modulation of adult hippocampal neurogenesis by thyroid hormones: implications in depressive-like behavior. Molecular Psychiatry. 2006;11:361-371. DOI: 10.1038/sj.mp.4001809.
52. Alkemade A, Unmehopa U, Brouwer J, Hoogendijk W, Wiersinga W, *et al*. Decreased thyrotropin releasing hormone gene expression in the hypothalamic paraventricular nucleus of patients with major depression. Molecular Psychiatry. 2003;8:838-839. DOI: 10.1038/sj.mp.4001305.
53. Bauer M, Heinz A, Whybrow PC. Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. Molecular Psychiatry. 2002;7:140-156. DOI:10.1038/sj.mp.4000963.

54. Douma SL, Husband C, O'Donnell ME, Barwin BN, Woodend AK. Estrogen-related mood disorders: reproductive life cycle factors. ANS Advances in Nursing Science. 2005;28:364-375.
55. Krishnan V, Nestler EJ. Linking molecules to mood: new insight into the biology of depression. American Journal of Psychiatry. 2010;167:1305-1320. DOI: 10.1176/appi.ajp.2009.10030434.
56. West D, Favero J, Aulchenko Y, Oswald P, Souery D, *et al*. A major SNP haplotype of the arginine vasopressin 1B receptor protects against recurrent major depression. Molecular Psychiatry. 2004;9:287-292. DOI: 10.1038/sj.mp.4001444.
57. De Winter R, Hemert A, DeRijk R, Zwinderman K, Frankhuijzen-Sierevogel A, *et al*. Anxious–retarded depression: relation with plasma vasopressin and cortisol. Neuropsychopharmacology. 2003;28:140-147. DOI: 10.1038/sj.npp.1300012.
58. Londen L, Kerkhof G, Berg F, Goekoop J, Zwinderman K, *et al*. Plasma arginine vasopressin and motor activity in major depression. Biological Psychiatry. 1998;43:196-204.
59. Verster GC. Melatonin and its agonists, circadian rhythms and psychiatry. African Journal of Psychiatry. 2009;12:42-46.
60. Lamont EW, Legault-Coutu D, Cermakian N, Boivin DB. The role of circadian clock genes in mental disorders. Dialogues in Clinical Neuroscience. 2007;9:333-342.
61. Girish M, Bhuvana K, Nagesh Raju G, Sarala N. A novel atypical antidepressant drug: Agomelatine - A review. International Journal of Pharmacology and Biomedical Research. 2010;1:113-116.
62. Soria V, Urretavizcaya M. Circadian rhythms and depression. Actas Españolas de Psiquiatría. 2009;37:222-232.
63. Jacobsen J, Medvedev I, Caron M. The 5-HT deficiency theory of depression: perspectives from a naturalistic 5-HT deficiency model, the tryptophan hydroxylase 2Arg 439 His knocking mouse. Philosophical Transactions of the Royal Society. 2012;367:2444-2459. DOI: 10.1098/rstb.2012.0039.
64. Yildiz A, Gonul A, Tamam L. Mechanism of actions of antidepressants: Beyond the receptors. Bulletin of Clinical Psychopharmacology. 2002;12:194-200.
65. Kasper S, Hamon M. Beyond the monoaminergic hypothesis: Agomelatine, a new antidepressant with an innovative mechanism of action. The World Journal of Biological Psychiatry. 2009;10:117-126. DOI: 10.1080/15622970801909585.
66. Klemens J. Herbs used for psychotropic or behaviour modifying activity. Journal for the American Association of Integrative Medicine; c2006. p. 1-9.
67. Bach-Rojecky L, Kalodjera Z, Samarzija I. The antidepressant activity of *Hypericum perforatum* L. measured by two experimental methods on mice. Acta Pharmaceutica. 2004;54:157-162.
68. Dhingra D, Sharma A. A review on antidepressant plants. Natural Product Radiance. 2006;5:144-152.
69. Mamedov N. Adaptogenic, geriatric, stimulant and antidepressant plants of Russian Far East. Journal of Cell and Molecular Biology. 2005;4:71-75.
70. Mesfin F, Demissew S, Teklehaymanot T. An ethnobotanical study of medicinal plants in Wonago Woreda, SNNPR, Ethiopia. Journal of Ethnobiology and Ethnomedicine. 2009;5:28. DOI: 10.1186/1746-4269-5-28.
71. Getahun A. Some common medicinal and poisonous plants used in Ethiopian folk medicine. Addis Ababa University, Addis Ababa, Ethiopia; c1976.
72. Eitan R, Lerer B. Nonpharmacological, somatic treatments of depression: electroconvulsive therapy and novel brain stimulation modalities. Dialogues in Clinical Neuroscience. 2006;8:241-258.
73. Cusin C, Dougherty D. Somatic therapies for treatment-resistant depression: ECT, TMS, VNS, DBS. Biology of Mood & Anxiety Disorders. 2012;2:14. DOI: 10.1186/2045-5380-2-14.
74. Gotto J, Rapaport M. Treatment options in treatment-resistant depression. Primary Psychiatry. 2005;12:42-50.
75. Londen L, Kerkhof G, Berg F, Goekoop J, Zwinderman K, *et al*. Plasma arginine vasopressin and motor activity in major depression. Biological Psychiatry. 1998;43:196-204.
76. Verster GC. Melatonin and its agonists, circadian rhythms and psychiatry. African Journal of Psychiatry. 2009;12:42-46.
77. Lamont EW, Legault-Coutu D, Cermakian N, Boivin DB. The role of circadian clock genes in mental disorders. Dialogues in Clinical Neuroscience. 2007;9:333-342.
78. Girish M, Bhuvana K, Nagesh Raju G, Sarala N. A novel atypical antidepressant drug: Agomelatine - A review. International Journal of Pharmacology and Biomedical Research. 2010;1:113-116.
79. Soria V, Urretavizcaya M. Circadian rhythms and depression. Actas Españolas de Psiquiatría. 2009;37:222-232.