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Review Article

MEDICINAL HERBS AND PHYTOCHEMICALS USED IN THE TREATMENT OF DEPRESSION: A REVIEW

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ABSTRACT

Depression is a condition of no mood and loss of interest in any activity that can diminish a person's thinking, conduct, tendencies, emotional state, and a sense of well-being. Although there is a conventional class of medication which have been beneficial in the treatment of depression, current studies have reported having side effects which can be minimized by the intervention of herbs and phytochemicals. Most of the studies have proven the various mechanisms and have started to research a very ground-breaking method by glancing the ancient treatmen. Where this new approach of using the herbs and phytochemicals has shown better results alone and in combination with conventional drugs which has shown lesser adverse effects. The practice of phytomedicine is an additional option for the treatment of depression. In the various segments of treating the depression, the mainstream can be a breakthrough including phytoconstituents. In this aspect, there are many contributions for the treatment of the depression acting to the neuronal level signaling and the phytoconstituents also have shown some basic mechanisms in the treatment of depression as that of the conventional medications following some primary hypothesis and signaling pathways and life interactions that effects the brain in either way to treat the depression in all sort of way. Clinical evidence is required to provide backing to the safety and effectiveness of herbs and phytochemicals alone or in combination with currently available drugs to overcome the reported side effects during the treatment of depression.

Keywords: Phytoconstituents, Interventional therapy, Phytomedicine.

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INTRODUCTION

Depression is a condition of no mood and loss of interest to activity that can lessen a person's thinking, conduct, tendencies, emotional state, and sense of well-being which has shown morbidity worldwide [1]. It has even reported as one of the prevailed psychiatric disorders which have been estimated as the second most significant contributor to neurological diseases and disability worldwide [2]. According to the World Health Organization Global Burden of Disease, depression has been predicted to become the second cause of long-term debility in 2020 and the primary cause by 2030 [2]. Depression is one of the highly prevailed neuropsychiatric disorders which has 40.5% of all disability attuned life years caused due to mental pathologies [3]. Major depressive disorder is a mental disease with clinical manifestations indulging anorexia, insomnia, loss of interest, and continuous sadness, where in contrast there may be hyperphagia, and motor agitation in addition. Depression can be managed by medications (pharmacological treatment), psychotherapy (cognitive behavioral therapy and interpersonal therapy), and electroconvulsive therapy. One potential method also involves the use of medicinal herbs and phytochemicals that provide therapeutic benefits with minimal adverse drug reaction [4]. The main cause or the origin of the depression can be from the gene level. It can be from the family twin or adoption. The genetic factors have the effect of 30–40% in depression. Other factors contribute to 60–70% to depression. Non-genetic factors are mainly socioeconomical causes which affect the population ranging from 15 to 45 years including marital problems, divorce, lifetime trauma, low social support, interpersonal adversities, childhood sexual abuse, and loss of loved ones [5]. Depressogenic effects mainly can be gender specific with the high alterations in the average level such as men get affected by separation, work difficulties, and low income.

Meanwhile, women get affected by severe illness or death. The causes are many whereas the symptoms will be specific [6]. The sensory nervous system mainly senses various responses from the environment such as death, social stress, and retort to injuries in the human body, and then the sequenced information is carried out by the emotional circuits in the brain [7]. Since then there is no proper information regarding neuronal loops possessing the pathophysiology of the brain in depression (Table 1), the effort is made to note the significant hypothesis and some regions on depression [8]. The brain of a human was subjected to many types of research to have various alterations in the hippocampus, amygdala, striatum, prefrontal cortex, and cingulate cortex and many more, these irregularities in the brain were seen in a depressed patient during autopsy [9].

Types Depression [10]

Persistent depression

It is the mood that lasts for couple of years maybe two or three. A patient diagnosed with this depression have various symptoms with long term effects on behaviour

Postnatal depression

After getting a baby some women will get this type of depression. It is also called "Baby Blues". It is comparatively a lite depression and anxiety that clears within two weeks after delivery.

Bipolar depression

It includes the extremely low moods and euphoric or irritable conditions hence it is called It includes the extremely low moods and euphoric or irritable conditions hence it is called Maniac depression.

Seasonal effective disorder

It is also known to be "winter depression". Usually occurs during winter season due to less light. It is mainly occurred with weight gain, increased sleep, and social withdrawal.

Medicinal herbs and phytochemicals used in depression

There are so many categories of conventional antidepressants used against depression such as Tri-cyclic antidepressants, monoamine

oxidase (MAO) inhibitor, and second-generation antidepressants. The MAO inhibitor block serotonin transporter (SERT), norepinephrine, which enhances their synaptic levels where it shows improvement neurotransmission. Monoamine inhibitors consist of tranylcypromine, phenelzine, isocarboxazid, and moclobemide are given as first-line therapy [30]. These inhibitors block norepinephrine and SERTs which shows enhancement of their level and increase in transmission. These chemicals increase the activity of neurotransmission [31].

Then, the second-generation antidepressants comprise serotonin-norepinephrine reuptake inhibitors norepinephrine reuptake inhibitors, the selective serotonin reuptake inhibitors. Although there is so much of advancement in the field of medicine, there is a drawback in the treatment of depression, and there is a failure to remission of the disease [32,33]. Moreover, there are still cases like so many; adverse events have been causing for the patients from various types of the system like refractory responsiveness. There are so many adverse effects caused by these drugs such as tachycardia, tremor, sedation, insomnia, serotonin syndrome, anxiety, diaphoresis, postural hypotension blurred vision, Parkinson, and others [34,35].

All this research envisaged have seen alterations in the accumulative up gradation in the treatment with high adverse effects. Phytomedicine and medicinal herbs are one of the oldest ways of approach, but due to the fast medicine, the system has got buckled. However, now in recent days due to a higher number of adverse effects, this system of approach has got more importance due to less adverse effects and potent action as that of conventional antidepressants [36,37].

Medicinal herbs used in the treatment of depression

Herbs are one of the basic sources of medication used in ancient medicine. It is gaining one of the main prominences in the treatment of depression. Moreover, many studies have shown that there was an improvement in depression with the treatment of herbal medication. Some medicinal herbs have shown the effects as that of the antidepressants lately. The psychopharmacological actions against the nervous system by the medicinal herbs also have the same effects as that of the antidepressants which help in regulating the serotonin, dopamine, and noradrenaline reuptake, where it also helps in the MAO inhibition and modulation of neuroendocrine system along with hypothalamic-pituitary-adrenal (HPA) axis [38], there are some of the herbal medication which has been listed below and can be used in the treatment of depression.

Green tea

Camellia sinensis is commonly known as green tea. Where it is a herb generally known for its antioxidant property. The main bioactive constituents of green tea are caffeine, Theanine, xanthine, proteic, and nonproteinous amino acids and polyphenols where xanthine is a nonselective inhibitor of $A2_A$ and A receptors, which assists in performing the reduction of the excitatory neurotransmitter release and inflammatory responses and apoptosis which are some of the cause of depression [39].

Theanine is one of the main bioactive constituent that has shown higher antioxidant property and excellent antinflamatory action. Where it has shown excellent results in treatment with the synergistic action of theanine and caffeine with the elevated component polyphenols, the other main components present in the green tea are catechins, epicatechins, and epicatechins 5-gallate epigallocatechins [40].

The brain is vulnerable to various kinds of diseases like oxidative stress which is caused mainly due to the high amount of intake of oxygen free radicles in the neurons, which mainly serves as a prominent cause for the depressive-like behavior. In addition to this, there will be a release of excitatory neurons and dysfunction of mitochondria and drastic changes in the blood–brain barrier. Where the cause as the research says the gamma-aminobutyric acid (GABA) A receptor dysfunction, all these abruptions in the brain may be treated by the green tea with its various components such as polyphenols, catechins, and caffeine by elevating the serum level of corticosterone and by regulating the HPA axis with its action by decreasing the oxidative stress by its antioxidant property [41].

St. John's wort

Hypericum perforatum is also called St. John's wort. In the present studies, it has shown that medicinal form of St. John's wort comprises various leaves and flowering tops with the components of xanthones, naphthodianthrones, flavonoids, phloroglucinols (hyperforin), and hypericin. Latest researches have shown that *H. perforatum* has shown the improvement in depression like that of typical antidepressants selective serotonin reuptake inhibitors, and tricyclic antidepressants [42]. *H. perforatum* can inhibit the monoamine neurotransmitters such as 5-hydroxytryptamine (5-HT), noradrenaline, and dopamine where it increases the concentration of other monoamines and serotonin in various extracellular space in a brain such as thalamus, amygdala, hippocampus, and the prefrontal cortex [43]. Upregulation of the 5-HT receptors is one of the primary functions of the *H. perforatum* which, in turn, has the effects of upregulation of the neurons, in turn, leading into a factor of dopamine reducing the background firing in the neurons. This herb also have its effects in the upregulation of the factor in 5-HTA_A receptors as that of the SSRIs; it also has its effects in blocking the binding of GABA3, which has the effects in the reduced storage capacity of the central nervous system (CNS). *H. perforatum* has its effects in N-methyl-D-aspartate receptors (NMDARs) which has its necessary action as that of the nootropics [44].

Many studies have shown that the main constituents of this herb which are hypericum and hyperforin have a major effect in the neuronal transmission like; hypericum has its structure similar to that of MAO inhibitors which suppress the release of the interleukin 6, where interleukin 6 is one of the substances that help in the inflection of the cortisol release, reuptake inhibition of dopamine, norepinephrine, serotonin, and gamma-aminobutyric acid by hyperforin [41].

Lavender

Lavender is a herbaceous plant known as *Lavandula angustifolia*, with the recent researches it has shown that lavender in aromatherapy has shown

Table 1: Pathophysiology of Depression

Hypothesis	Theory stated
Neuronal atrophy	Reduction in the flow of blood, metabolism of glucose, and hence in the parts of the hippocampus and prefrontal cortex the volume will be reduced [10]
BDNF role	Reduction in the level of protein primarily in the dentate gyrus of the hippocampus and BDNF mRNA in the neuronal junctions [11]
Variability in gene	Proper research has been made from twin studies that 30–40% of depression will be from variations in the genes [12]
Stress hormones and cytokines	Increased functional activity of MG and reduced limbic GR receptor function system suggests an imbalance in MG/GR ratio in the stress-related condition that leads to depressive disorder [13]
Role of monoamines	Exhaustion of neurotransmitters such as noradrenaline serotonin, or dopamine in the central nervous system and improper functioning of the central noradrenergic system [14]
Neurotrophic hypothesis	The decrease in the hippocampal BDNF level [15]
Circadian rhythms	Damage in the sleep-wake directive in depressed patients can be daytime variations in psychomotor activity and mood fluctuations in the convenience of memories of positive and negative experiences [16]

GR: Glucocorticoid, BDNF: Brain-derived neurotrophic factor

Table 2: Novel perspective of various mechanisms in depression:

Mechanisms	Theory
Ketamine and other non-selective NMDAR antagonists	Dysfunction of the glutamatergic system was a profound action on the depression, where the NMDARs are a grounding system for the treatment of depression [17]. Ketamine one of the rapid NMDAR antagonists shown to have a rapid action on the depression Ketamine acts by elevating the presynaptic glutamate release, ensuing instigation of Akt and an extracellular signal associated with kinase (extracellular signal-regulated kinase) signaling, which, in turn, stimulates mTOR signaling [18]. The activation of mTOR signaling increases the downstream synaptic protein synthesis by phosphorylation of kinase and inhibiting the binding protein Hence, ketamine modulates mTOR signaling by increasing BDNF [19]
Selective NMDAR subtype 2B (NR2B) antagonists	Among all the NMDAR subtypes, NMDAR subtype 2B is of the efficient receptor that expresses in the forebrain and is associated with NMDA neurotoxicity genetic obliteration of NR2B from the principal of cortical neurons with the suppression of the behavior by elevating the mTOR action in the synaptic protein synthesis. Where traxoprodil is a selective NR2B antagonist [20,21]. All these studies were conducted on experimental mouse models
NMDA Partial agonists	NMDA partial agonists are usually comprehended as NMDAR modulators because they have agonist action in lesser doses. Hence, NMDA agonists are considered as latent antidepressants[22] D-cycloserine is one of the NMDA partial agonists where diminished long-term potentiation in the neural cell connexion in the molecule inadequate mice model[23] Where D-cycloserine increases the expression of Arc protein, which was associated with memory amalgamation [23]
NK 1 antagonists	NK 1 antagonists is a neuromodulator and a neurotransmitter which acts on NK 1 receptors Where the initial excitement about conjectural antidepressant properties of NK-1 which was decreased in a clinical trial study [23]
Orexin signaling activation	Orexin signaling is a well-known function which regulates the consolidation of stimulation of metabolism regulation, regular food intake, and mediating responses Although orexin lack is not a sole reason for depression, many preclinical studies have been made for the symptoms[24] Ghrelin is a peptide hormone produced by ghrelin cells in the gastrointestinal tract and functions a neuropeptide in the central nervous system where Ghrelin plays a significant role in regulating the distribution rate, whereby inducing effective feeding response and the use of energy[25] in response of energy shortage, orexin neuron will induce an active nourishing reaction by triggering growth hormone which secretes ghrelin receptors that exits in the central nervous system[26] Ghrelin which activates the neurons via c-FOS expression in the orexin cells, by the polymorphism detected the number of depressive cases was treated with ghrelin administration, which has shown an elevation in the mood of the patient [27]
Transcranial magnetic stimulation	Although electroconvulsive therapy has cognitive shortfalls, the stimulation of the safer brain has been formed by tedious TMS, which was approved by the FDA for the treatment of depression [28] This therapy stimulates the neurogenesis, and in some studies, it was proved that TMS modulates the amygdala by increasing neurotransmitters such as serotonin and dopamine [29]

mTOR: Mammalian target of rapamycin, BDNF: Brain-derived neurotrophic factor, NMDAR: N-methyl-D-aspartate receptor, Arc: Activity-regulated cytoskeletal, NK 1: Neurokinin 1, TMS: Transcranial magnetic stimulation

outstanding results as a hypnotic and mild sedative, and the women who have undergone delivery were shown positive response toward their infants and have overcome postpartum depression. The active ingredients of lavender that is linalool and linalyl acetate which has shown rapid absorption in the plasma peak have been proven in the recent study [45]. Most of the therapy given by lavender is shown to be aromatherapy where it has even shown its effects on the respiration during the sleep has improved the quality of sleep by suppressing the cause of insomnia. Where the studies even have shown the significant effects on the increased 2nd stage of the sleep. Where the sleep was successfully induced with the elevation in the mood, and there were no side effects reported, which indirectly gives a betterment of depression by modulating the circadian rhythm[46].

The essential oil in *L. angustifolia* has a significant effect in the CNS with the popular target areas such as GABA A, SERT, MAO-A, and NMDARs; recent studies have shown that lavender even exhibits its action on the dose-dependent characteristics with the significant effects on glutamate NMDARs by showing its affinity. The lavender possesses the other major component that is linalool which was even bound to SERT, the primary context of the whole theme is due to SERT inhibition and NMDAR antagonism (Table 2) [47].

Ginseng

Panax ginseng is a botanical name of ginseng and is mainly used to treat clinically. It was one the best medicine in past years, Where in recent days, several pieces of research have confirmed that ginseng has shown antidepressant-like activity with its component ginsenosides in experimental animal models. There are many causative factors for the induction of the depression like Glial cells aggregation along with blocking the neuronal cells, but the recent studies have shown that glial cells have astrocytes which show an major role in the pathogenesis of depression [48]. Where ginseng effectively regulates the response in the immune system and it has also helped in maintaining the homeostasis. In addition to the psychological diseases, it has shown various effects in treating depressive-like disorders. Recent studies have shown that ginseng is involved in the treatment of the HPA axis, like the HPA axis and also involved in the controlling of the hormones which are beneficial for the further process. The cortisol is mainly produced and regulated in the control center of the brain that is HPA axis and also regulated by the sympathetic nervous system [49].

The HPA axis plays an essential role in regulating all the endocrine glands related to the CNS, where ginseng regulates the chronic inflammation through the HPA axis to inhibit various disorders, mainly depression. However, there is no reference as such for the potential biomarking of the HPA axis by ginseng since the studies are still on progress. However, the ginseng has demonstrated various levels of the efficacy in many levels of the process. The neuroprotective effect of the ginseng has various effects enhanced ameliorate anxiety with depression [50].

Lemon balm

Lemon balm is also called *Melissa officinalis* it is an ancient drug, which was very reliable during the curative treatment from the ancient times. *M. officinalis* has shown high phenolic content and has a vigorous property of antioxidant. Lemon balm has even demonstrated the antioxidant property and immune modulating property, which has a property of autoxidation and EDTA-mediated oxidation by linoleic acid [51]. The free radicle scavenging property of the lemon balm is very known action as an antioxidant and its significant effect in the neurotransmitter due to radicles rush in the presynaptic junction. There are many streams of pathways describing the uses of lemon balm, where the concentration variations of monoamines like serotonin (5-HT) in the CNS. The selective serotonin in the CNS was checked by the antioxidant property [52].

Lemon balm is a tranquilizing antioxidant. It was shown that it has a benefit of exhaustion in the nervous tissue. *M. officinalis* herb generally acts on the brain tissue with its property of blood–brain barrier crossing capacity. It generally falls to the category of green tea. Furthermore, it has proven to show a synergistic effect [53].

Cocoa

Cocoa is obtained from *Theobroma cacao* where many types of research have proven that cacao is a polyphenolic compound and was proven to have a calming effect, due to its affinity for adenosine and GABA receptors. There are many pieces of evidence stating that cocoa affects cognitive performance and an increase in cerebral blood flow. Cocoa-derived products have discovered to have a high level of flavonoids and to have antioxidant property [54]. Where many studies have proven that phenolic cocoa extract was shown to have a protective effect on neurons and has even revealed an increase in neurotransmitters including the rise in the serotonin levelse. The ingestion of this carbohydrate may cause an increase in serotonin and neurotransmitter has stated to have a significant role in the psychopharmaceutical target [55]. Some studies have stated that ingestion of carbohydrates with some 6% of protein there was an increase in the serotonin synthesis that may be due to the protein which has relatively less tryptophan than any amino acids with a very high range of blood tryptophan induced secretion of insulin.

As the research says, chocolate composition is not the same where there is no certainty. However, many studies have hypothesized that chocolate is rich in sugar but less protein that has favored the serotonin synthesis [56].

Ashwagandha

Withania somnifera is also called Ashwagandha where it is considered as an adaptive and was mainly used to diminish and accelerate the hypothalamic-pituitary thyroid neuroendocrine axis where that has been associated with the pathogenesis of major depression. Ashwagandha is shown as "adaptogen" which means that it has a magnificent antioxidant property, and referred to as neuroprotective, anti-inflammatory and has a perfect memory enhancing property [56]. Withania somnifera crosses the blood brain barrier. Where many clinical studies have been proven that *W. somnifera* can withstand all the stressors and help to regulate the psychological process, by acting on GABA with receptor binding receptor in many animal models [57].

W. somnifera has also been used in the treatment of cerebrospinal fluid (CSF) GABA level elevation and the correlation between GABA-CSF concentration and clinical status. This has led to the preliminary indication disconcerted GABAergic transmission and GABA-mimetic agents in an animal model [58].

Roseroot

Rhodiola rosea known as the rose root is the phytomedicine which has an adaptogenic property and is effective in treating moderate depression. The range of depressive disorder that has a major level of biochemical imbalances of monoamine like epinephrine, norepinephrine, and serotonin [59]. Although psychopharmaceutical drugs appear to have an essential role in the treatment of depression, the current study status has an extent of research. The standardized root extracts serotonin-5, including the neurotransmitter levels and in the CNS [60].

R. rosea is system-stimulating serotonin-5 and the nervous treatment system with the process of oxidative deamination and peripheral tissue. The level of MAO_A inhibitors has shown to be active and often associated with pharmacological treatment [61].

Phytochemicals used against depression

L-theanine

L-theanine is an amino acid obtained from *C. sinensis* which is also known as green tea. Where L-theanine emerges to be a nonproteinous amino acid and has a fantastic property of crossing the blood–brain barrier and proven to be elevated to the brain in a dose-dependent manner. Many preclinical studies on rats have been made to check the attenuation of hippocampal CA1 long-term potentiation after the exposure to the stress-induced suppression of recognition memory was rescued by L-theanine [62]. The cognitive dysfunction on the mice was found to be more effective by the treatment of L-theanine and its antidepressant effects. The antidepressant effect of L-theanine together with NMDARs has shown agonist action. In healthy humans, L-theanine has shown better effects in the reduction of anxiety and depression has been scored. L-theanine was proven to decrease the sympathetic nerve responses [63]. Many studies have proved that electroencephalogram studies have affected both the sites and α-wave including the influence prefrontal cortisol function, having the dominant effect on the cognitive impairment and process associated with the memory impairment [64].

In most of the studies, the mainstream of the depression was affected by the prefrontal cortex, and magnetic resonance spectroscopy has revealed that patients with the depressive disorder have the exhibited the increase in the level of glutamate in the hippocampus region. Where L-theanine is an amino acid shown exhibit the alterations and profiles through competitive inhibition of the transporters which, in turn, has influenced the transporters and neurotransmitter function [65].

Carvacrol

Carvacrol is an aromatic herb obtained from oregano and thyme. The carvacrol is a significant constituent seen in essential oils and aromatic plants. It has shown various properties on cognition and has a significant effect on the depression. Besides, it was proven to be the chemical flavonoid, and the safety index is yet to be proved. Many clinical studies have been done using carvacrol as it acts on estrous stage specific in the depressed women patient and it has exhibited its effect by serotonin and metabolite tissue content in the prefrontal cortex and nucleus acumens the involvement in the serotonergic system [66].

The carvacrol is a monoterpenoid phenol which, in turn, regulates the human ion channels and transient receptor potential and has a significant effect in the V3 and A1 potential causing the warmth. The carvacrol has a significant property of activation of the peroxisome proliferator-activated receptor and to subjugate the cyclooxygenase - 2 mediated depression [67]. The carvacrol on the administration has proven to act on the dopaminergic brain pathways and rise in the 5-HT and dopamine ranges and prefrontal cortex [68].

Curcumin

Curcumin is obtained from *Curcuma longa* also known as turmeric. Where it has a mechanism of antidepressant activity and is inhibited by MAO A and B here the phytochemical has proven to show the elevation of neurotransmitter level in the brain. The antidepressant effects of curcumin have shown to represent the significant hypothesis of depression that is the cytokine hypothesis and monoamine hypothesis [69]. Where curcumin has shown the increase in the concentration of monoamine which is available to interact with the receptors and has shown the elevation similarly as that of the tricyclic antidepressants [70].

The mechanism has even stated that curcumin is proven to show anti-inflammatory activity as that of the hypothesis of cytokine, which has raised the crucial role in the development of the major depressive disorder. Besides, the curcumin has strongly inhibited the anti-inflammatory cytokines like a nuclear factor that is kappa B and NLRP3 inflammasome and interleukin-1B. Curcumin from the long back has proven to be a neuroprotective alongside conventional therapy in the trails [71]. Furthermore, the laboratory studies have been proven to exhibit the behavioral changes in the HPA axis and the brain-derived neurotrophic factor (BDNF). A new approach to the medical stream was found by treating the synthetic drug along the side of a natural herb or the phytochemical [72]. It was extensively started proving from the drug of curcumin, and the action proved to be synergistic. The large-scale sequenced treatment alternatives to relieve depression and due potential have a chance of balancing the monoaminergic pathways and HPA axis disturbances [73].

Ferulic acid

Ferulic acid is an organic compound mainly found in seeds, leaves, and plant cell walls. The ferulic acid has been reported to have various neurotherapeutic effects concerning the ameliorative action on glutamate excitotoxicity along with apoptosis and high reactive oxygen species (ROS) level [74]. The enhancement of the indoleamine 2,3-dioxygenase action in the brain resulting in the atypical shift of tryptophan metabolism near to kynurenine away from serotonin. Where the reduction in the brain levels explains the effectiveness of drugs and has to be elevated where ferulic acid has shown its action as an antidepressant [75]. The primary study was done that depressant patients tended to show the effects on the system by the overproduction of glucocorticoids has involved in the antioxidant defense and reduction and hyperactivation of NMDAR leading to cell death. Most of the treatment used in the treatment of depression will be through, a monoaminergic system [76].

The research has stated significant evidence that ferulic acid is a phenolic compound that is widely distributed in many species of plant, counting many grains, fruits, and vegetables which can reach the blood-brain barrier. Ferulic acid is a well-known antioxidant and a glutamate correspondent molecule that gives protection in contradiction of glutamatergic excitotoxicity which indicates an NMDAR antagonism effect [75].

Proanthocyanidin

Proanthocyanidin is an oligomeric and polymeric flavan-3-ol found in various plants including apple, cocoa, bean, grape, and tea [77]. The studies have proved that there will be overexpression of pro-inflammatory cytokines in the hippocampus, prefrontal cortex, and amygdala were these are reversed by proanthocyanidin [78].

Proanthocyanidin is a protectant acts an antioxidant and also helps in the reduction of glutathione along with glutathione peroxidase, superoxide dismutase, and catalase enzyme in the liver [79,80]. Where proanthocyanidin has a property as a natural antioxidant and keeps ROS scavenging action. Proanthocyanidin has shown superior scavenging contrary to hydroxyl radicals and as compared to both Vitamin C and Vitamin E [81].

Resveratrol

Resveratrol is a natural phenol found in grapes and red wine. Resveratrol has an outstanding property of neuroprotective [82,83]. The resveratrol has a significant effect on the regulation of antioxidant effect by ameliorating the hyperactivity of the HPA axis, and resveratrol is also testified for the metabolism of the noradrenaline and serotonin and acts as another antidepressant. The mainstream of proving the action of resveratrol is by its BDNF modulation in the brain. It has been shown that the resveratrol has been occupied the dominant stream in acting as a neuroprotective agent with the huge ability to escalate the neurogenesis, with many other disorders in the brain. Resveratrol has also proven to show the action as the best sleep inducer with anti-aging property [48,84]. In addition to the system, monoaminergic and molecular markers are related to depression which has a complication with both hypothalamic-pituitary-thyroid axis and HPA axis [79,80].

In many studies, the resveratrol has proven to have an action on 5-HT and noradrenaline to restore the normal monoaminergic function and to produce the antidepressant activity by BDNF involved expression in the system [85].

CONCLUSION

From past centuries, the knowledge about the herbs has proven to be beneficial to humankind. The whole system was followed with a basic concept of curing the disease in the intensely passionate form of the way with the available resources around us. Now in a recent decade, there is an advancement wherein the system there is scope for the phytochemicals which is obtained from the different sources. All these herbs and phytochemicals above mentioned will come under various hypothesis and mechanisms of depression. Where there are some herbs like green tea where the photochemical like L-theanine is extracted, which, in turn, has a preferment with the elevation in the concentration of neurotransmitters or inhibition of the neuronal apoptosis.

As abridged here, the preclinical and clinical studies have proven the mechanism on which these drugs tend to act on the human brain to repose the depression and its symptoms. The primary cause of using the phytomedicinal herbs and chemicals is because it does not have the adverse effect as that of the counterfeit medicine used in the treatment of depression. The other cause of using the phytomedicine maybe it is pocket-friendly because of the whole system of costing much money for the conventional drugs to obtain it from the market which may be not be affordable by the ordinary people. Since the safety index is useful in treating the patients with phytomedicine, as these herbs and phytomedicine have shown positive results in a preclinical stage with both *in vivo* and *in vitro.* However, clinical studies are taken aback. While the efficacy and the potency of phytomedicine have to be supported by the clinical studies and the mechanisms of these drugs should be tamed well.

CONFLICTS OF INTEREST

All authors have none to declare.

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