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Review Article

Herbal Psychiatric Disorder

# A Review on Herbal Drugs Used For the Treatment of Psychiatric Disorder

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**Abstract:** Only one-third of persons with psychiatric conditions such as bipolar disorder, psychosis, stress, anxiety, and depression get complete treatment, and the danger of relapse still exists. Additionally, they may result in several negative side effects, including impotence, constipation, dry mouth, and tiredness. Researchers are now looking for more specialized medications that are safer and cheaper. Researchers in this discipline has been interested in medicinal plants because they have historically been used to treat various illnesses, including mental problems, and because they have fewer side effects than synthetic & chemical medications. Western drugs have a wide range of adverse effects, and the number of individuals who experience them is rising. A comprehensive study on the use of herbal medicine for depression, anxiety, and sleeplessness is still missing. This review, which was carried out better to define the mechanisms of action of various herbal medicines, offers helpful data regarding the use of herbal medicine. Research on distress is abundant, but it's important to consider how well herbal remedies work for these conditions. Traditional medical systems are still used extensively on many fronts. Increased emphasis has been placed on using plant materials as a source of medicines for a wide range of human maladies as a result of factors like population growth, an inadequate supply of medications, prohibitive costs of treatments, side effects of some synthetic drugs, and the emergence of drug resistance to currently prescribed medications for infectious diseases. Objective- The overview covers all the pertinent topics in herbal treatment today, including safety concerns and potential future applications.

**Keywords**: Depression, Bipolar Disorder, Herbal Medicine, Insomnia, Mechanism, Psychopharmacology.

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## 1. INTRODUCTION

One of the most prevalent neuropsychiatric conditions, depression accounts for 40.5% of the years of disability-adjusted life caused by psychological illnesses. At some point in their lives, 20% of the population will have a significant depressive episode. Depression is a widespread, chronic, complex illness that poses a serious risk to life. Currently, depression is one of the top 10 killers in the world, affecting 29% of the population. In affluent nations, depression will rank second in terms of illness burden in 2020, according to the WHO.[1] Depression impacts sufferers' friends and relatives in addition to themselves. The primary signs and symptoms of depression include social disengagement, loss of motivation, dysfunctional sexual behaviour, sleep difficulties (75% of patients), nightmares, a sad mood, and anhedonia. In addition, 15% to 25% of depressed people also exhibit sadism and suicide ideas. [2] Depression develops as a result of several causes, including biological, genetic, and psychological. Internal stresses, such as changes in blood levels of sugar, coagulation factors, cholesterol, and triglycerides, have recently been revealed to have a role in the onset of depression.[3] Depression is now treated with several medications, such as lithium salts, tricyclic antidepressants, stimulants, serotonin blockers, and monoamine oxidase inhibitors. To lessen unwanted side effects or have a faster recovery, many individuals with psychotic disorders turn to unconventional drugs or therapies.[4] Complementary and alternative medicine (C.A.M.) and therapeutic lifestyle changes are examples of non-conventional medicine.[5] For diverse (cultural or practical) reasons, complementary medicine consists of diagnostics, treatments, and prevention methods based on biomedical theories and supported by some empirical evidence (two or more randomized controlled trials [R.C.T.s]).[6] Diagnostics, therapies, and preventative measures used in alternative medicine go beyond the fundamental principles of biomedicine. However, there is currently minimal evidence supporting the effectiveness of the latter treatments, and there is significant disagreement on their scientific validity.[7] Utilizing substances made by living organisms (plants, trees, seeds, vegetables, fruits, animals, and people) rather than synthetic (i.e., chemical) substances that can only be obtained by laboratory testing, natural medicine is a form of supplemental medicine. Some patients prefer natural remedies because they believe they are superior and will have fewer side effects. Since substances in the natural environment can be hazardous to humans, it is evident that this is not always the case. Instead of its source, a substance's impact on human health is determined by its molecular makeup and dosage.[7] Additionally, herbal remedies may have negative side effects, such as drug interactions.[8] This review article aims to investigate the biological components of medicinal plants that have an antidepressant impact and their mechanisms of action and antidepressant effects.

### *1.1 Herbal remedies commonly used to treat the psychiatric symptom*

#### *1.1.1 Withania somnifera.*

Small shrubs called "Ashwagandha," also known as "Withania somnifera" or "Winter Cherry," may be found in the drier regions of India, Pakistan, Afghanistan, Sri Lanka, the Democratic Republic of the Congo, South Africa, Egypt, Morocco, and Jordan.[9] One of the most effective herbal medicines used in Indian traditional medicine (Ayurveda) is Ashwagandha (roots of Withania Somnifera DUNAL), which is used as a rasayana medication to promote long life, young vitality, and strong mental faculties. These historical usages suggest that Ashwagandha may aid in the treatment of neurodegenerative disorders. The pharmacological properties of this herbal medicine have been documented to include anti-inflammatory, anti-tumour, antioxidant, immunomodulatory, and actions against neuropsychiatric diseases, Withaferine A and withanolide D, the plant's two primary withanolides, account for the majority of its pharmacological effects.[10] Significantly effective anti-stress properties have been found for the sitoindosides IX -X and withaferin-A.[11] Withania somnifera (L.) extract is a complex combination of several phytochemicals, such as alkaloids. In addition to treating tumours, alkaloids treat diarrhoea and nocturnal leg cramps brought on by vascular spasms. These substances have sedative and anti-microbial properties. Many alkaloids are anaesthetics that have soothing effects on people who are psychotic or have high blood pressure but do not put them to sleep. Alkaloids may also be utilized to treat palpitations and psychological conditions. Various substances, including flavonoids, steroidal lactones, steroids, salts, and nitrogen-containing compounds, cause intestinal, uterine, tracheal, and vascular smooth muscle contractions. It has been reported that the total alkaloids extracted from the extract of W.S. roots have relaxant and antispasmodic effects against these substances. The plant has yielded more than 12 alkaloids, 40 withanolides, and several sitoindosides, which have all been isolated and documented. We describe the effects of herbal drugs used to treat depression, anxiety and mood disorder like Bipolar disorder, Schizophrenia etc. Evidence from previously reported clinical trials suggests that W.S.E. has antianxiety properties in participants who are stressed, participants reporting anxiety and those with diagnosed anxiety disorders.[12,13]

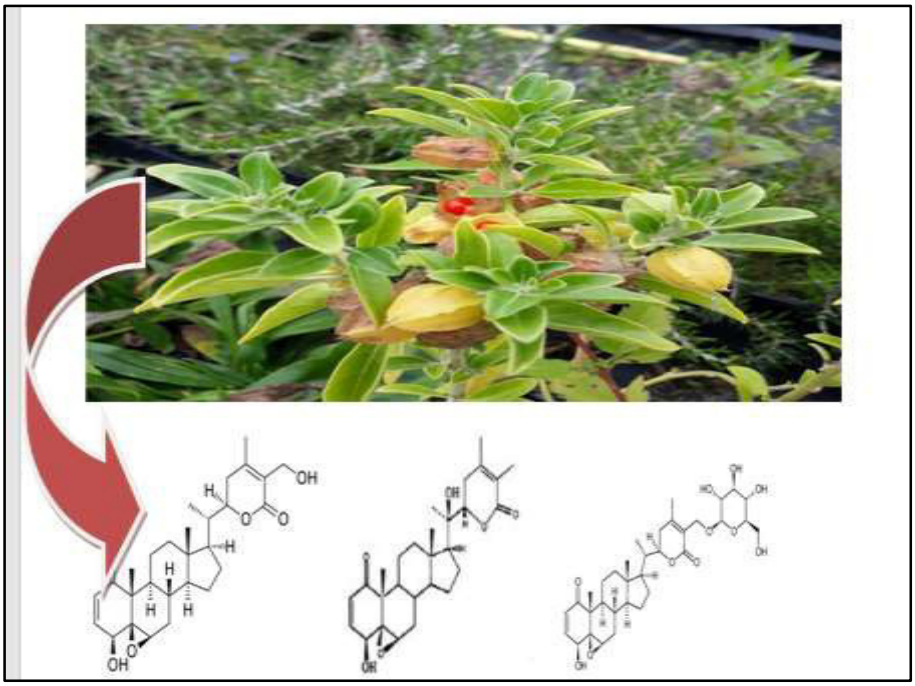


**Fig.1 Phtoactive constituents of Withania Somnifera**

### *1.2 Gingko biloba.*

Ginkgo biloba (Ginkgoaceae family), also known as maidenhair tree, is native to East Asia but grows prolifically in Europe and America. This ancient tree has been profusely used in Chinese, Japanese and Indonesian traditional medicine.[14] Gb extract contains mainly terpenoids, flavonol glycosides, and proanthocyanidins. The flavonol glycosides (quercetin, catechin) are the most prevalent of these three groups. The terpenoids include ginkgolides and bilobalides, which represent unique components of G.B.E. The antioxidant-containing G.B.E. improves cognitive function in Alzheimer's disease (A.D.), Parkinson's disease (P.D.), peripheral vascular diseases, and neurosensory problems (e.g., tinnitus) with mixed results. Ginkgo biloba has positive effects on psychosis, anxiety, Schizophrenia, and depression (saki et al., 2016). It stimulates cerebral blood circulation and improves problems caused by the failure of blood circulation in the brain, including anxiety, stress, low memory, hearing problems, low concentration, thinking social behaviour, and dementia in Alzheimer's disease.[15]

**Table 1. Metabolites & Active constituents of Ginkgo biloba with Pharmacological activity**

| Metabolite substances | Active constituents | Pharmacological activity |
|---|---|---|
| Terpenoids | Ginkgolide<br>Ginkgolide B<br>Ginkgolide C | They enhance the memory in the A.D. model by increasing the cholinergic transmission, which is shown to reduce MPTP-induced nigrostriatal dopaminergic neurotoxicity in the P.D. mice model. It is also shown to decrease proinflammatory cytokine by suppressing of MAPK pathway in neurons.[16] |
| Flavonol glycosides | Quercetin<br>Kaempferol<br>Isorhamnetin<br>Glycosides | Anxiolytic activity that inhibits the enzyme FAAH reduces fear reaction.[17]<br>Antidepressant activity due to Increasing AKT/β-catenin cascade in the prefrontal cortex.[18] |

### *1.3 Ginseng (Panax quinquefolium).*

Ginseng is traditionally used as a medicinal herb in Korea, Japan, China, and the United States (Shahrajabian et al., 2019). The reason for this long-established usage is that ginseng contains natural antioxidant compounds. These ginsenosides, extracted from the ginseng roots, leaves, stems, and fruit, have multiple pharmacological effects. They are subdivided into about 100 different categories.[19] In many studies, ginsenosides have been presented as an effective treatment for organ damage and cell death and immunological and metabolic diseases. Numerous studies indicated ginseng promotes health and prevents potential disease, such as immune-modulatory, anti-inflammatory, lipid-lowering, anti-oxidation, anti-diabetic, anti-tumour, increases energy, medicine, anti-ageing, anti-depression, inhibit or delay the neurodegenerative process, improving memory and perceptual systems.[20]

**Table 2- M.O.A. of different Ginsenosides along with their Pharmacological action**

| Ginsenosides | Mechanism | effects |
|---|---|---|
| Ginsenoside Rg1 | Sustainable management of the potential of mitochondrial membrane ; ↓ an excessive inflow of Ca2+ into the mitochondria; ↑ Increasing energy output | ↑ Surviving plus neuritic development in cellular glutamate-induced Stress.[21] |
| Ginsenoside Re | ↓ TUNEL(+) ratio; TH(+) neurons; ↑ Bcl-2 mRNA and Bcl-2 protein expression; ↓ Bax, Bax mRNA, promotes expression of iNOS; ↓ Caspase-3 cleavage | ↓ MPTP-induced apoptosis in nigral neurons[22] |
| Ginsenoside Rd | ↑ The quantity of NeuN(+) neurons; ↓ NO synthesis, as well as PGE2 synthesis | Guard against LPS-induced neurotoxicity and neuro-inflammation.[23] |
| Ginsenoside Rb1 | ↑ Nuclear migration of PI3K and Nrf-2 (ER-dependent PI3K/Akt/G1/PI3K-Nrf2) signalling system) | ↑ antioxidant defences (like heme oxygenase-1) ↓ oxidative stress caused by 6-OHDA damage as well as apoptosis.[24] |
| Notoginsenoside R2 | ↓ Activation of ERK1/2 and Akt ↓ BAD; P90RSK; triggered by 6-OHDA mitochondrial depolarization of the membrane ↑ phase II detoxification and Nrf2 actions of enzymes; ↑ ERK1/2-MEK1/2 signalling | Prevention of 6-OHDA-induced mitochondrial apoptotic death.[25] |

### *1.4 Grapeseed oil and pycogenol*

Pycnogenol (P.Y.C.), a family of flavonoids isolated from French maritime pine bark (Pinus pinaster Aiton, synonym Pinus maritima Mill.), is a mixture of procyanidins with potent antioxidants and R.O.S. scavenging properties. P.Y.C. supplements may reduce depression-like behaviour in the CORT mice model by its antioxidant activity, suggesting that chronic treatment of CORT-induced mild stress-mediated depression-like behaviours as observed by F.S.T. and that the potent antioxidant activity of P.Y.C. can slightly decrease the progression of Psychiatric stress disorders are a wide range of disorders, including depression, anxiety, Schizophrenia, and bipolar, disrupting individual and social life. According to previous studies, GSE could attenuate anxiety and depression[26]. The grape seed proanthocyanidins ameliorate anxiety-like behaviour in animals.[27] it was previously reported that GSE could reduce anxiety and depression in middle-aged women. Therefore, this extract seems to be considered a valuable antidepressant and antianxiety agent. It has been revealed that GSE antidepressant property is exerted via hippocampal VGF.[28] V.G.F. (non-acronymic) is a neuropeptide precursor and has antidepressant efficacy. GSE has also been shown to have protective effects against stress-induced psychological disorders.[29]

**Table. 3 Polyphenol effects on Parkinson's diseases present in the Grape seed.**

| Polyphenols | Animal Model | Pharmacological effects | Preventive disorder |
|---|---|---|---|
| Proanthocyanidin[30,31,32] | PC12 cell line APP/PS-1 double transgenic mice | ↓ Amyloid plaques inside the hippocampus are lessened, cognitive function and spatial memory are improved, and the pathology of APP and tau protein is improved. Level of PS-1 mRNA expression. | A.D. |
| | | ↓ Prevention of dopaminergic neurons against 6-OHDA toxicity, apoptosis (cleaved caspase-3 activity), R.O.S. generation, inflammation (phospho-NF-B p65 activation), and other reactions. | |
| | Midbrain dopaminergic cell line – Adult male CD1 mice | ↓ Improvement in cognitive performance; generation of A; phosphorylation of tau; loss of neurons and apoptosis in the cerebral cortex and hippocampus tissue; and mitochondrial oxidative stress as well as mPTP opening ↓ (phosphorylation of PI3KAkt-GSK-3 pathway) in these tissues. | P.D. |
| | Primary mouse cortical neurons –Sporadic A.D. mice | | P.D. |

### *1.5 Licorice (Glycyrrhiza glabra, Liquiritia officinalis)*

Additionally, studies using mice in immobility tests and a passive avoidance procedure revealed that licorice had memory-improving effects.[33] In rats under long-term stress, a large number of G. Liquiritin, a component of uralensis, has been demonstrated to have antidepressant properties. The Forced Swimming Test (F.S.T.) and the Tail Suspension Test, two well-known mice, despair experiments, also demonstrated that liqueritin and isoliquiritin had an antidepressant-like effect (2008). (T.S.T.). The authors speculate that the elevated levels of norepinephrine and 5-hydroxytryptamine in the rat brain, hypothalamus, and hippocampus may represent the action mechanism of such substances. The second component in licorice, carbenoxolone, exhibited sedative and muscle-relaxant properties in mice and genetically epilepsy-prone rats (GEPRs).[34] In a study that examined the effects of glabra root extract on learning and memory in male Wistar albino rats one-month-old. It was discovered that doses of 150 and 225 mg/kg greatly enhanced memory and learning and were comparable to controls. They contend that this enhancement results from plant extract's anti-inflammatory & antioxidant properties, which lessen oxidative stress in delicate brain cells and result in less brain damage or even enhanced neuronal function.[35]

### *1.6 Hypericum perforatum*

Although it originated in Europe, H. perforatum, often referred to as St. John's wort in English, has spread far over the globe, particularly in temperate and subtropical areas like China, Turkey, Ukraine, Russia, India, Canada, as well as the United States. Several studies on the antidepressant effects of H. perforatum in mice and humans have confirmed the plant's potential therapeutic benefits.36 The treatment and recurrence prevention of depression is aided by H. perforatum extract. H. perforatum responds more slowly than citalopram does.[37] Biochemical investigations reveal that H. perforatum slows synaptosomal resorption of serotonin, dopamine, and norepinephrine while being a moderate monoamine oxidase inhibitor. Beta-adrenergic receptors are down-regulated by H. perforatum extract, whereas serotonin receptors are up-regulated, and neurotransmitter levels in certain brain regions are also affected. Additionally, H. perforatum methanolic extract increases the expression of genes that regulate the H.P.A. axis. In addition to reducing the symptoms of chronic stress-induced depression, research indicated that H. perforatum extracts at 150–75 mg/kg also decreased corticosterone and ACTH blood levels. This extract also improved the antioxidant defence system and decreased the inflammatory markers TNF- and IL-6. H. perforatum's antioxidant, anti-inflammatory, as well as endocrine system-regulating qualities were linked to the plant's depressive effects.[38] Hypericin, hyperforin, as well as isoquercetin, three compounds found in H. perforatum, have been shown to have antidepressant effects. Injections of hypericin decreased CRH and the synthesis of its related mRNA in depressed animals. The above ground components (flowers, leaves, & stems) were dried with 80% ethanol (vol/vol) before extraction. The ratio of herb to extract for a 100 per cent native extract is 12:1.

### *1.7 Piper methysticum G. Foster (Kava)*

The herbal medicine regulatory agencies have authorized P. methysticum G. Foster (kava) for the symptomatic relief of mild-to-moderate anxiety stages.[39] This species has also been associated with depression, anxiety, insomnia, and concurrent attention-deficit/hyperactivity disorder. Anxiolytic properties of the South Pacific herb kava have been utilized for generations. Kavalactones (or kavapyrones), like methysticin, kawain, dihydromethysticin, dihydrokavain, and yangonin, are among the beneficial compounds present in kava. Recent studies have shown that isolated kavalactones affect the 38/nuclear factor-kappaB/cyclo-oxygenase 2 signalling pathway. Methysticin and kavain bind to inactive sodium channels in kava and extend their inactivation, which inhibits voltage-gated ion channels. Kavalactones also stopped noradrenaline from being absorbed into rat cerebral cortex and hippocampus synaptosomes in vitro.[40] In addition, it was found that yangonin and dihydrodravanadin inhibit COX-1 and COX-2. In a clinical experiment carried out in 1996 by Lehmann and associates, it was discovered that Kava extract was more efficient than a placebo in treating individuals with anxiety.[41] Kava's calming effects on patients with generalized anxiety were further supported by meta-analysis research, which showed a substantial decrease in anxiety parameters as evaluated by the Hamilton Anxiety (HAMA) scale .[42]

### *1.8 Valeriana officinalis L. (Valerian)*

Valerian officinalis L. extracts alleviate mild sleep issues and emotional stress. The two extracts' potential for acting as an antidepressant and myorelaxant was evaluated using the forced swimming and horizontal wire tests. In contrast to its parent extract, phytofin Valerian 368 had an antidepressant effect following subacute therapy in the forced swimming test (a 35 per cent ethanolic extract). No myorelaxant effects were seen at doses as high as 1000 mg/kg bw. These findings suggest that the valerian's anxiolytic and depressive action, particularly discovered in the phytofin Valerian 368 extract, plays a significant role in the herb's ability to induce sleep.[43] Valerian officinalis L. extracts s.l. Demonstrate neither sedative nor myorelaxant qualities but antidepressant and anxiety-reducing effects (Phytomedicine).

### *1.9 St. John's wort (Hypericum perforatum)*

Although St. John's wort is well-recognized for treating depression, it is less well-known for reducing anxiety. Chronic Hypericum perforatum therapy had an antianxiety medication effect in the forced swim test, an anxiolytic effect in the elevated T-maze, and the light/dark transition test in rats with low magnesium levels. In animal models of restrained anxiety and sleep deprivation, St. John's wort therapy provides an antianxiety effect. Hypericum perforatum alters neuronal excitability and glutamatergic and GABAergic pathways to noradrenaline and diminishes serotonin and dopamine reuptake. There aren't many studies that thoroughly examine St. John's wort's impact on anxiety patients. The present study does not indicate the benefits of St. John's wort for anxiety disorders. St. John's wort is not useful in treating phobias, obsessive-compulsive disorder (O.C.D.), posttraumatic stress disorder, or generalized anxiety disorder in double-blind, randomized, placebo-controlled research. Hypericum extract significantly decreased anxiety levels on the HAMA scale in 149 patients with indistinguishable somatoform autonomic dysfunctions or somatoform disorder.[44] A 500-person uncontrolled open-label study found that St. John's wort extract helped patients with sadness and anxiety by lowering the symptoms of anxiety disorders. Before considering St. John's

wort as a treatment for those with diagnosed mental distress and depression, further study is necessary.

### *1.10 Valeriana officinalis*

Valerian root is one of the most popular herbal remedies for anxiety and insomnia.[45] Both aqueous and hydroalcoholic extracts of valerian roots exhibited an affinity for the GABA-A receptor in the rats' brains. [46] Valerian has been shown to help treat stress and human insomnia. Andreatini et al. (2002) compared Valerian officinalis L. to a placebo in people with G.A.D. Only the diazepam and valepotriates groups showed a significant reduction in the psychic component of the HAMA scale, and preliminary findings suggest that valepotriates may have a potential anxiolytic effect on psychic anxiety symptoms (DSM-III-R, 12 patients per group). Extract (81 mg of valepotriates as active components) to placebo and diazepam (6.5 mg). Due to the small sample size and low diazepam dosage employed in this study, it is recommended that comparable research be carried out again using a stronger scientific approach.[47]

### *1.11 Ginkgo biloba*

Ginkgo biloba extract, a potent antioxidant, may help to reduce depression-like behaviour. In a forced swim test, rats given EGb761 had a shorter immobility time, which is a sign of depressive-like behaviour. The survival instinct manifests itself in increased movement or attempts to swim in such a test. Less mobility, on the other hand, is associated with depression. The immobility associated with depressive-like behaviour was reduced in rats treated with ginkgo biloba extract. This indicates that EGb761 has antidepressant properties in the animal.[48] Mice were examined in an elevated plus-maze, and motor activity was measured to see if ginkgo biloba extract administration had anxiolytic-like effects. The activity of rats in each open arm of this maze is recorded and observed in each of the four arms. Antianxiety behaviour is seen in increased open-arm activity. The G.B.E. group had reduced motor activity, implying that ginkgo biloba extract has anxiolytic properties.

### *1.12 Matricaria recutita (chamomile)*

A randomized, double-blind, placebo-controlled trial of oral matricaria recutita (chamomile) extract therapy for generalized anxiety disorder suggests that one or more of its flavonoid constituents may have anxiolytic activity by altering the neurotransmission of -amino butyric acid (GABA), noradrenalin (N.A.), dopamine (DA), and serotonin.[49] It has also been shown that apigenin and other chamomile ingredients bind to B.Z. Receptors and inhibit GABA-activated action.Herbal teas, often known as tisanes, frequently include chamomile as a single component. For generations, gastrointestinal issues have been treated with chamomile tea, produced from dried flower heads. Other disorders it is used for include allergic rhinitis, attention deficit hyperactivity disorder (ADHD), restlessness, sleeplessness, dysmenorrhea, mastitis, and varicose ulcers. Chamomile contains flavonoids that have benzodiazepine-like effects and inhibit phosphodiesterase, which raises cAMP levels. In recent research, individuals with mild to moderate G.A.D. were given either a standardized extract of Matricaria recutita (L) or a placebo for eight weeks (DSM-IV). There was a statistically significant decline in HAMA ratings in the extract-treated group as compared to the placebo-treated group.[50]

### *1.13 Astragalus membranaceus*

The popular Korean herb Astragalus membranaceus (AM) has been utilized in the past to cure ailments brought on by stress. AM significantly improves learning and memory deficits in mice who have been subjected to ongoing stress. Furthermore, AM treatment significantly lengthens the time spent in the open arms in the raised plus maze compared to the control group. Additionally, it increased choline acetyltransferase (ChAT) expression in stressed rats.[51] There is no scientific proof that it has anxiolytic properties. Astragalous, however, has been discovered in a clinical investigation to have a protective effect on oxidative stress in hemodialysis patients.

### *1.14 Rhodiola rosea L. (Rose root)*

R. Rosea may be beneficial for treating depression via known psychopharmacological actions, including neuroendocrine modulation (inhibition of cortisol, stress-induced protein kinases, nitric oxide), monoamine oxidase A inhibition, monoamine modulation, normalization of 5-HT, and anti-stress effects in animal depression models.[52] over six weeks, a phase III clinical trial was conducted as a randomized, double-blind placebo-controlled study with parallel groups. Eighty-nine patients with mild to moderate depression were randomly assigned to either the placebo or the active treatment. Over six weeks, extract SHR-5 at 340 or 680 mg/day. Individuals with Overall depression, insomnia, emotional instability, and somatization, but not self-esteem, improved significantly after treatment in the SHR-5 groups, whereas the placebo group did not. There were no serious side effects reported in any of the groups.[53]

### *1.15 Herbal remedies that may cause psychiatric symptoms*

#### *1.15.1 Ginseng*

P ginseng is frequently mistaken for E senticosus (Siberian ginseng). CA Meyer (also known as ginseng, Chinese ginseng, Korean ginseng, or P quinquefolius L, sometimes known as Canadian ginseng or American ginseng) and P quinquefolius L has a vast number of uses, some of which include alleviating fatigue and stress and enhancing endurance.[54] Despite the several proposed modes of action, it most likely impacts the hypothalamic-pituitary-adrenal axis, causing higher plasma corticotropin and corticosteroids. One of the most frequent adverse effects is sleeplessness, along with others, including euphoria, anxiety, restlessness, diarrhoea, hypertension, and anxiety.[55] Patients with diabetes and hypertension should use ginseng with caution, as should those taking other drugs with central actions. Additionally, ginseng may enhance the effects of haloperidol, M.A.O. inhibitors, and stimulants (including caffeine).[56]

### *1.16 Yohimbe*

The bark of the P yohimbe (K Schum) tree is the source of the herbal remedy known as yohimbe (Pausinystalia yohimbe [K Schum]).[57] The alkaloids are the active ingredients, particularly yohimbine, a yohimbane derivative. The hydrochloride salt of yohimbine is utilized in treating erectile dysfunction because it appears to work as an $\alpha_2$ adrenoceptor antagonist.[58,59] Yohimbe bark is frequently sold for this use since it is thought to have aphrodisiac characteristics. Yohimbine is a drug that, when

given to humans, produces several symptoms, including anxiety, jitters, palpitations, and restlessness, as well as indicators such as increased levels of 3-methoxy-4-hydroxyphenylglycol and cortisol. Yohimbine is actually one of the substances that are frequently used to induce anxiety and panic episodes in research on the psychopharmacology, pathophysiology, and therapy of anxiety disorders.[60]

## 2. CONCLUSION

This is to be concluded that enormous herbal plant is widely used to prevent and cure depression, anxiety and psychiatric illness. However, their pharmacokinetic parameters are still not fully evaluated due to fewer clinical trials and studies. The toxicological profile is still not fully investigated, which may lead to an adverse drug reaction. The dose is highly contradicted, and unclear what dose is needed for a particular illness. It also needs to investigate the quality, efficacy and safety issues to prevent from their adverse drug reaction. Most of the Phyto-active constituents showed improved mental illness when prescribed adjunct therapy for psychiatric illness. Standardization of herbal drugs is limited by WHO to comply with avoiding toxicity during clinical research. Furthermore, a study is needed to elaborate on the pharmacological intervention of these herbal drugs.

### *1.17 Limitations*

Numerous neurodegenerative illnesses have unknown origins. Since many decades ago, herbal medicine has attracted considerable interest due to its medicinal potential. Due to their anti-inflammatory, antioxidative, and anticholinesterase properties, phytochemicals are likely promising treatments for neurodegenerative illnesses. The cellular and subcellular characteristics of neurodegenerative diseases, including A.D., PD, Huntington's, and others, are similar, as are the majority of the molecular signalling pathways that might result in apoptosis, necroptosis, and inflammation. In general, using herbal medicine offers hopeful substitutes for the present treatments for neurodegenerative illnesses. However, the poor pharmacokinetic qualities of herbal medicine/natural substances severely limit their potential.

## 3. AUTHOR CONTRIBUTION STATEMENT

M.R.I.: conceptualization, Resources, Material, Data collection or processing, Writing manuscript, Critical review; GA.: Design, Analysis. M.K.S.: Literature search

## 4. CONFLICT OF INTEREST

Conflict of interest declared none.

## 5. REFERENCES


1. Abbasi Maleki S, Bekhradi R, Asgharpanah J, Abbasi Maleki F, Maleki A. Antidepressant effect of aqueous and hydroalcoholic extracts of Lavandula officinalis in forced swim test and tail suspension test in male mice. J Arak Univ Med Sci. 2013;16:65-75.
2. Ahmad H, Rauf K, Zada W, McCarthy M, Abbas G, Anwar F et al. Kaempferol facilitated extinction learning in contextual fear conditioned rats via inhibition of fatty-acid amide hydrolase. Molecules. 2020 Jan;25(20):4683. doi: 10.3390/molecules25204683, PMID 33066366.
3. Alrefaie Z. Grape seed proanthocyanidins Attentuate anxiety-like behavior in an experimental model of dietary-induced hypercholesterolemia in rats. Int J Vitam Nutr Res. 2016 Jul 14;1(1):1-0.
4. Kulkarni SK, Dhir A. Withania somnifera: an Indian ginseng. Prog Neuropsychopharmacol Biol Psychiatry. 2008 Jul 1;32(5):1093-105. doi: 10.1016/j.pnpbp.2007.09.011, PMID 17959291.
5. Hoenders R. Integrative psychiatry. Conceptual foundation, implementation and effectiveness. Inintegr Psychiatry Conceptual Found Implement Eff. 2013:(212-).
6. Hoenders HJ, Appelo MT, van den Brink EH, Hartogs BM, de Jong JT. The Dutch Complementary and Alternative Medicine (C.A.M.) protocol: to ensure the safe and effective use of complementary and alternative medicine within Dutch mental health care. J Altern Complement Med. 2011;17(12):1197-201. doi: 10.1089/acm.2010.0762, PMID 21506670.
7. 7, Topliss JG, Clark AM, Ernst E, Hufford CD, Johnston GA, Rimoldi J.M. et al. Natural and synthetic substances related to human health [IUPAC technical report]. Pure and Applied Chemistry. Vol. 74(10); 2002 Jan 1. p. 1957-85.
8. Ernst E. Serious psychiatric and neurological adverse effects of herbal medicines–a systematic review. Acta Psychiatr Scand. 2003 Aug;108(2):83-91.
9. Hazra M, Noh S, Boon H, Taylor A, Moss K, Mamo DC. Complementary and alternative medicine in psychotic disorders. J Complement Integr Med. 2010 Sep 4;4(1):7(1). doi: 10.2202/1553-3840.1239.
10. Duggal S, Singh H, Singh J, Withanolides KS: Phytoconstituents with significant pharmacological activities. 5Singh A. Int J Green Pharm (IJGP). 2010;4(4).
11. Bhattacharya SK, Goel RK, Kaur R, Ghosal S. Anti-stress activity of sitoindosides VII and VIII, new acylsterylglucosides from Withania somnifera. Phytother Res. 1987 Mar;1(1):32-7. doi: 10.1002/ptr.2650010108.
12. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med. 2012 Jul;34(3):255-62. doi: 10.4103/0253-7176.106022, PMID 23439798.
13. Cooley K, Szczurko O, Perri D, Mills EJ, Bernhardt B, Zhou Q et al. Naturopathic care for anxiety: a randomized controlled trial ISRCTN78958974. PLOS ONE. 2009 Aug 31;4(8):e6628. doi: 10.1371/journal.pone.0006628, PMID 19718255.

14. Sun B, Dilcher DL, Beerling DJ, Zhang C, Yan D, Kowalski E. Variation in Ginkgo biloba L. leaf characters across a climatic gradient in China. Proc Natl Acad Sci U S A. 2003 Jun 10;100(12):7141-6. doi: 10.1073/pnas.1232419100, PMID 12777617.
15. Nah SY, Kim DH, Rhim H. Ginsenosides: are any of them candidates for drugs acting on the central nervous system? C.N.S. Drug Rev. 2007 Dec;13(4):381-404. doi: 10.1111/j.1527-3458.2007.00023.x, PMID 18078425.
16. Dey A, Nath De J.N. Possible anti-Parkinson's disease therapeutics from nature: a review. Stud Nat Prod Chem. 2015 Jan 1;44:447-520. doi: 10.1016/B978-0-444-63460-3.00009-2.
17. Ong WY, Farooqui T, Koh HL, Farooqui AA, Ling EA. Protective effects of ginseng on neurological disorders. Front Aging Neurosci. 2015 Jul 16;7:129. doi: 10.3389/fnagi.2015.00129, PMID 26236231.
18. Pan Y, Wang J, Gao J, Li H, Chen H. Study on the Network Pharmacological Mechanism of Huanglian Wendan decoction in the treatment of depression; 2022.
19. Kim yh. ginsenosides from heat-processed korean ginseng roots, leaves and flower buds. inpharmaceutical biology 2012 may 1 (vol. 50, no. 5, pp. 569-570). telephone house, 69-77 paul street, london ec2a 4lq, england: informa healthcare.
20. Rajabian A, Rameshrad M, Hosseinzadeh H. Therapeutic potential of panax ginseng and its constituents, ginsenosides and gintonin, in neurological and neurodegenerative disorders: a patent review. Expert Opin Ther Pat. 2019 Jan 2;29(1):55-72. doi: 10.1080/13543776.2019.1556258, PMID 30513224.
21. Radad K, Gille G, Moldzio R, Saito H, Ishige K, Rausch WD. Ginsenosides Rb1 and Rg1 effects on survival and neurite growth of MPP+-affected mesencephalic dopaminergic cells. J Neural Transm (Vienna). 2004a;111(1):37-45. doi: 10.1007/s00702-003-0063-1, PMID 14714214.
22. Xu BB, Liu CQ, Gao X, Zhang WQ, Wang SW, Cao YL. Possible mechanisms of the protection of ginsenoside Re against MPTPinduced apoptosis in substantia nigra neurons of Parkinson's disease mouse model. J Asian Nat Prod Res. 2005;7(3):215-24. doi: 10.1080/10286020410001690172, PMID 15621629.
23. Lin WM, Zhang YM, Moldzio R, Rausch WD. Ginsenoside Rd attenuates neuroinflammation of dopaminergic cells in culture. J Neural Transm Suppl. 2007;72:105-12.
24. Hwang YP, Jeong HG. Ginsenoside Rb1 protects against 6-hydroxydopamine-induced oxidative stress by increasing hemeoxygenase-1 expression through an estrogen receptor-related PI3K/Akt/Nrf2-dependent pathway in human dopaminergic cells. Toxicol Appl Pharmacol. 2010;242(1):18-28. doi: 10.1016/j.taap.2009.09.009.
25. Meng XB, Sun GB, Wang M, Sun J, Qin M, Sun XB. P90RSK and Nrf2 activation via MEK1/2-ERK1/2 pathways mediated by notoginsenoside R2 to prevent 6-hydroxydopamine-induced apoptotic death in SH-SY5Y cells. Evid Based Complement Alternat Med. 2013;2013:971712. doi: 10.1155/2013/971712, PMID 24159358.
26. Mei L, Mochizuki M, Hasegawa N. Pycnogenol ameliorates depression-like behavior in repeated corticosterone-induced depression mice model. BioMed Res Int. 2014 Jan 1;2014:942927. doi: 10.1155/2014/942927, PMID 24901001.
27. Alrefaie Z. Grape seed proanthocyanidins Attentuate anxiety-like behavior in an experimental model of dietary-induced hypercholesterolemia in rats. Int J Vitam Nutr Res. 2016 Jul 14;1(1):1-0.
28. Jiang C, Sakakibara E, Lin WJ, Wang J, Pasinetti GM, Salton SR. Grape-derived polyphenols produce antidepressant effects via V.G.F.- and BDNF-dependent mechanisms. Ann N Y Acad Sci. 2019 Nov;1455(1):196-205. doi: 10.1111/nyas.14098, PMID 31074515.
29. Sreemantula S, Nammi S, Kolanukonda R, Koppula S, Boini KM. Adaptogenic and nootropic activities of aqueous extract of Vitis vinifera (grape seed): an experimental study in rat model. BMC Complement Altern Med. 2005;5(1):1. doi: 10.1186/1472-6882-5-1, PMID 15656916.
30. Wang Y, Wang Y, Shen W, Wang Y, Cao Y, Nuerbulati N et al. Grape seed polyphenols ameliorated dextran sulfate sodium-induced colitis via suppression of inflammation and apoptosis. Pharmacology. 2020;105(1-2):9-18. doi: 10.1159/000501897, PMID 31743904.
31. Lian Q, Nie Y, Zhang X, Tan B, Cao H, Chen W, et al. Effects of grape seed proanthocyanidin on Alzheimer's disease in vitro and in vivo. Exp Ther Med. 2016 Sep;12(3):1681-92. doi: 10.3892/etm.2016.3530, PMID 27588088.
32. Sun Q, Jia N, Li X, Yang J, Chen G. Grape seed proanthocyanidins ameliorate neuronal oxidative damage by inhibiting GSK-3β-dependent mitochondrial permeability transition pore opening in an experimental model of sporadic Alzheimer's disease. Aging (Albany, NY). 2019 Jun 24;11(12):4107-24. doi: 10.18632/aging.102041, PMID 31232699.
33. Dhingra D, Sharma A. Evaluation of antidepressant-like activity of glycyrrhizin in mice. Indian J Pharmacol. 2005 Nov 1;37(6):390. doi: 10.4103/0253-7613.19077.
34. Gareri P, Condorelli D, Belluardo N, Russo E, Loiacono A, Barresi V et al. Anticonvulsant effects of carbenoxolone in genetically epilepsy prone rats (GEPRs). Neuropharmacology. 2004 Dec 1;47(8):1205-16. doi: 10.1016/j.neuropharm.2004.08.021, PMID 15567430.
35. Chakravarthi KK, Avadhani R, Narayan RS. Effect of Glycyrrhiza glabra root extract on learning and memory in Wistar albino rats. Drug Invent Today. 2012 Aug 5;4(7):387-90.
36. Butterweck V, Schmidt M. St. John's wort: role of active compounds for its mechanism of action and efficacy. Wien Med Wochenschr. 2007 Jul;157(13-14):356-61. doi: 10.1007/s10354-007-0440-8, PMID 17704987.
37. Singer A, Schmidt M, Hauke W, Stade K. Duration of response after treatment of mild to moderate depression with Hypericum extract S.T.W. 3-VI, citalopram and placebo: A reanalysis of data from a controlled clinical

trial. Phytomedicine. 2011;18(8-9):739-42. doi: 10.1016/j.phymed.2011.02.016, PMID 21514125.

38. Grundmann OL, Lv Y, Kelber O, Butterweck V. Mechanism of St. John's wort extract (STW3-VI) during chronic restraint stress is mediated by the interrelationship of the immune, oxidative defense, and neuroendocrine system. Neuropharmacology. 2010 Mar 1;58(4-5):767-73. doi: 10.1016/j.neuropharm.2009.12.014, PMID 20036263.
39. Fajemiroye JO, da Silva DM, de Oliveira DR, Costa EA. Treatment of anxiety and depression: medicinal plants in retrospect. Fundam Clin Pharmacol. 2016 Jun;30(3):198-215. doi: 10.1111/fcp.12186, PMID 26851117.
40. Singh YN, Singh NN. Therapeutic potential of kava in the treatment of anxiety disorders. C.N.S. Drugs. 2002 Nov;16(11):731-43. doi: 10.2165/00023210-200216110-00002, PMID 12383029.
41. Wu D, Yu L, Nair MG, DeWitt DL, Ramsewak RS. Cyclooxygenase enzyme inhibitory compounds with antioxidant activities from Piper methysticum (kava-kava) roots. Phytomedicine. 2002;9(1):41-7. doi: 10.1078/0944-7113-00068, PMID 11924763.
42. Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: systematic review and meta-analysis. J Clin Psychopharmacol. 2000 Feb 1;20(1):84-9. doi: 10.1097/00004714-200002000-00014, PMID 10653213.
43. Hattesohl M, Feistel B, Sievers H, Lehnfeld R, Hegger M, Winterhoff H. Extracts of Valeriana officinalis L. sl show anxiolytic and antidepressant effects but neither sedative nor myorelaxant properties. Phytomedicine. 2008 Jan 25;15(1-2):2-15. doi: 10.1016/j.phymed.2007.11.027, PMID 18160026.
44. Volz HP, Murck H, Kasper S, Möller HJ. St John's wort extract (LI 160) in somatoform disorders: results of a placebo-controlled trial. Psychopharmacology. 2002 Nov;164(3):294-300. doi: 10.1007/s00213-002-1171-6, PMID 12424553.
45. Donath F, Quispe S, Diefenbach K, Maurer A, Fietze I, Roots I. Critical evaluation of the effect of valerian extract on sleep structure and sleep quality. Pharmacopsychiatry. 2000 Mar;33(2):47-53. doi: 10.1055/s-2000-7972, PMID 10761819.
46. Benke D, Barberis A, Kopp S, Altmann KH, Schubiger M, Vogt KE et al. GABAA receptors as in vivo substrate for the anxiolytic action of valerenic acid, a major constituent of valerian root extracts. Neuropharmacology. 2009 Jan 1;56(1):174-81. doi: 10.1016/j.neuropharm.2008.06.013, PMID 18602406.
47. Andreatini R, Sartori VA, Seabra ML, Leite JR. Effect of valepotriates (valerian extract) in generalized anxiety disorder: a randomized placebo-controlled pilot study. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. Phytother Res. 2002 Nov;16(7):650-4. doi: 10.1002/ptr.1027, PMID 12410546.
48. Rojas P, Serrano-García N, Medina-Campos ON, Pedraza-Chaverri J, Ögren SO, Rojas C. Antidepressant-like effect of a Ginkgo biloba extract (EGb761) in the mouse forced swimming test: role of oxidative stress. Neurochem Int. 2011;59(5):628-36. doi: 10.1016/j.neuint.2011.05.007, PMID 21672588.
49. Mao JJ, Li QS, Soeller I, Rockwell K, Xie SX, Amsterdam JD. Long-term chamomile therapy of generalized anxiety disorder: A study protocol for a randomized, double-blind, placebo-controlled trial. J Clin Trials. 2014 Nov;4(5). doi: 10.4172/2167-0870.1000188, PMID 29057164.
50. Amsterdam JD, Li Y, Soeller I, Rockwell K, Mao JJ, Shults J. A randomized, double-blind, placebo-controlled trial of oral Matricaria recutita (chamomile) extract therapy of generalized anxiety disorder. J Clin Psychopharmacol. 2009 Aug;29(4):378-82. doi: 10.1097/J.C.P.0b013e3181ac935c, PMID 19593179.
51. Sarris J, Panossian A, Schweitzer I, Stough C, Scholey A. Herbal medicine for depression, anxiety and insomnia: a review of psychopharmacology and clinical evidence. Eur Neuropsychopharmacol. 2011;21(12):841-60. doi: 10.1016/j.euroneuro.2011.04.002, PMID 21601431.
52. Sarris J, Stough C, Bousman CA, Wahid ZT, Murray G, Teschke R et al. Kava in the treatment of generalized anxiety disorder: a double-blind, randomized, placebo-controlled study. J Clin Psychopharmacol. 2013;33(5):643-8. doi: 10.1097/J.C.P.0b013e318291be67, PMID 23635869.
53. Darbinyan V, Aslanyan G, Amroyan E, Gabrielyan E, Malmström C, Panossian A. Clinical trial of Rhodiola rosea L. extract SHR-5 in the treatment of mild to moderate depression. Nord J Psychiatry. 2007;61(5):343-8. doi: 10.1080/08039480701643290, PMID 17990195.
54. Hiai S, Yokoyama H, Oura H. Features of ginseng saponin-induced corticosterone secretion. Endocrinol Jpn. 1979;26(6):737-40. doi: 10.1507/endocrj1954.26.737, PMID 396151.
55. Scaglione F, Cattaneo G, Alessandria M, Cogo R. Efficacy and safety of the standardized ginseng extract G115 for potentiating vaccination against the influenza syndrome and protection against the common cold [corrected]. Drugs Exp Clin Res. 1996;22(2):65-72. PMID 8879982 [published correction appears in Drugs Exp Clin Res. 1996;22:338].
56. Mitra SK, Chakraborti A, Bhattacharya SK. Neuropharmacological studies on panax ginseng. Indian J Exp Biol. 1996;34(1):41-7. PMID 8698406.
57. Tyler V. Herbs of choice: the therapeutic use of phytomedicinals. Binghamton, NY: pharmaceutical products press. Vol. 209; 1994.
58. De Smet PAGM, Keller K, Hansel R, Chandler R. Adverse effects of herbal drugs. Berlin, Germany: Springer Verlag; 1997. p. 250.
59. Lambert GA, Lang WJ, Friedman E, Meller E, Gershon S. Pharmacological and biochemical properties of isomeric yohimbine alkaloids. Eur J Pharmacol. 1978;49(1):39-48. doi: 10.1016/0014-2999(78)90220-0, PMID 658127.
60. Rasmusson AM, Southwick SM, Hauger RL, Charney DS. Plasma neuropeptide Y (N.P.Y.) increases in humans in response to the alpha 2 antagonist yohimbine. Neuropsychopharmacology. 1998;19(1):95-8. doi: 10.1016/S0893-133X(97)00199-1, PMID 9608581.