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REVIEW ARTICLE

Role of Phytoflavonoids in the Management of Anxiety and Depression: An Overview

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Abstract

The main global health issue, anxiety, and depression have significant psychological, social, and financial repercussions. It promotes an anticipatory and adaptable reaction to difficult or stressful situations. When anxiety is excessive, it destabilizes the person, which leads to a dysfunctional state. In the absence of intense situations, it's a pathological state. It comprises posttraumatic stress disorder, general anxiety, aversion to social situations, obsessive-compulsive disorder, and panic disorder. Some people think about using natural therapies as an alternative to anxiety drugs because they may cause negative side effects. Due to their natural origins and lack of adverse effects, these medications and herbal medicine are becoming more and more popular in both developed and developing nations. Minerals, organic matter, and medicinal plants are the sources of many traditional remedies. Alkaloids, also saponins, glycosides, flavonoids, which, etc. are all present. The goal of this summary is to provide in-depth knowledge about the many phytoconstituents that have the potential to reduce anxiety and play a significant role in CNS activity.

Keywords: Anxiety, Depression, Flavonoids, Medicinal Plants, Phytoconstituents, Traditional Medicine

1. Introduction

Over the past ten years, a growing body of evidence has emerged connecting abnormalities of the oxidative process to anxiety-related illnesses[1], high levels of anxiety[2], and sadness[3]. Depression and anxiety may coexist; depression is characterized as an anti-depressive state in psychiatric nosography, which makes coping harder[4]. People in contemporary culture experience a variety of psychiatric problems, particularly sadness, anxiety, and sleeplessness. Depressive disorders, one of the most common types of mental disease, have a significant impact on people and society. By the year 2024[5], Major Depressive Disorder (MDD) would rank as the second most common disease worldwide, according to the World Health Organization (WHO). Evidence linking abnormalities of oxidative metabolism to anxiety disorders[6], extreme anxiety, and depression has grown during the past ten years[7]. In what is known as an anxious-depressive syndrome in psychiatric nosography, anxiety, and depression may coexist and make coping more challenging[8]. The therapy of anxiety disorders involves the use of several herbs. Anxiety problems are treated with herbs including lemon balm, Brahmi, ginseng, passionflower, and Valerian. In clinical use, current pharmacological methods for managing anxiety have not yet produced the desired effects[9]. Natural herbal blends are regarded as nature-based modern pharmaceuticals since they work synergistically to give an effective treatment for anxiety[10].

2. Herbal Psychopharmacological

Likely, controlling a single target may not exert the antipsychotic effect as effectively as targeting many systems due to the complexity of psychiatric diseases. Herbal medicine is frequently used to treat mental illnesses through a variety of processes that act on multiple systems. Considering that neurological factors

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underlie mental disorders like depression, anxiety, and insomnia, which are frequently found in the same patient, it is likely that the mechanisms of treatment for these illnesses are intertwined. When certain factors act on one target, activity in a different area may manifest. Of course, this could affect how other mental diseases that are connected are treated[11].

3. Medicinal Herbs are Used in the Treatment of Anxiety and Depression

One of the primary sources of medicine in traditional Chinese medicine is herbs. It is becoming increasingly important in the management of anxiety and depression. Furthermore, numerous research studies have demonstrated that using herbal medicines to treat depression leads to improvements in the condition. Recently, certain therapeutic herbs have demonstrated effects similar to those of antidepressants. Some of the herbal medications that have been listed below and can be used in the treatment of anxiety and depression share similar psychopharmacological effects to those of antidepressants in that they help to regulate the serotonin, dopamine, and noradrenaline reuptake, where they also aid in MAO inhibition and modulation of the neuroendocrine system along with the Hypothalamic-Pituitary-Adrenal (HPA) axis[12].

4. Pathogenesis of Anxiety

In comparison to depression, anxiety's aetiology is less well understood and remains anxiety. abolished. However, recent research suggests that anomalies in noradrenergic, serotonergic, GABAergic, and glutamatergic communication are part of the pathophysiology of anxiety[13]. The effectiveness of sedatives, selective serotonin reuptake inhibitors, and selective serotonin and noradrenalin inhibitors of reuptake in the management of depression reflects the participation of this system[14].

5. Pathogenesis of Depression

The pathophysiology of depression has recently been centred on secondary messenger malfunction, monoamine impairment, and decreased monoamine production[15]. The importance of neuroendocrinological abnormalities, such as cortisol overabundance cytokine or steroid changes, modifications to neurotransmitters such and/or glutamatergic delivery, diminished natural opioid operation, and abnormal rhythms, has also received more attention in recent years[16] (Figure 1).

6. Mechanism of Action Herbal Medicines

There are several biological effects on the reuptake and receptor binding of different monoamines, frequently along with endocrine and psychoneuroimmunological regulation, which make the antidepressant modes of action of herbal medications less well understood than those of synthetic drugs[17]. Certain herbal remedies with anti-depressant properties, like *H. perforatum*, the cultivar *Crocus sativus* (saffron) (*C. sativus*) and rose root (*R. rosea*) (roseroot), offer favourable outcomes for the medical management of mood disorders via referred to psychopharmacological acts such as reducing amine re-uptake (noradrenaline, serotonin, and dopamine), the activity of monoamine oxidase inhibition, stimulation, and enhancement of serotonin receptor binding, or neuroendocrine modulation[17]. GABAergic effects, morphine, cannabinoid system effects, and other effects have also been proposed[18] (Figure 2).

7. Herbal Plants with Anxiolytics and Antidepressants Activity

One of the primary sources of medicine in traditional Chinese medicine is herbs. It is becoming increasingly

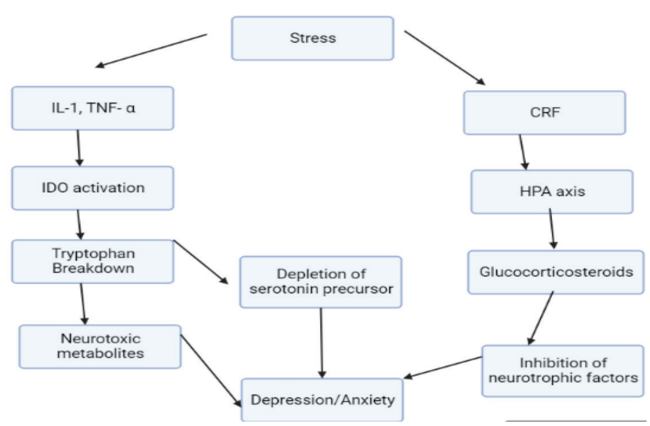

Figure 1. Pathogenesis of anxiety and depression.

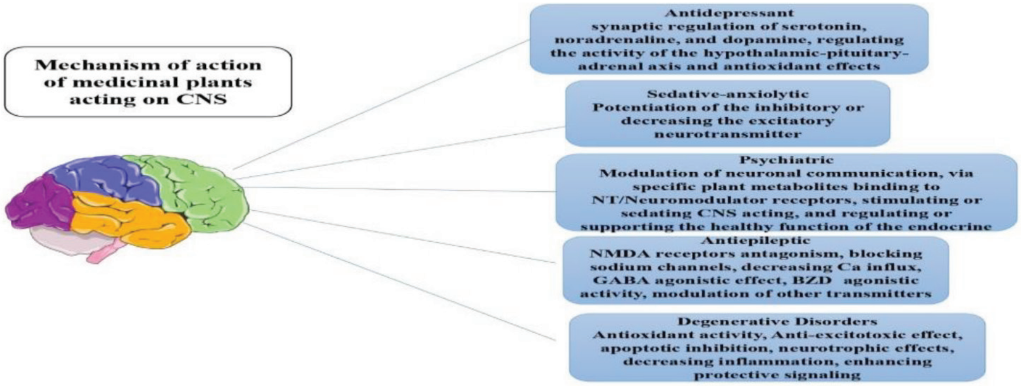

Figure 2. The mechanism of action of central nervous effects of medicinal plants.

important in the management of depression and anxiety. Furthermore, numerous research has demonstrated that using herbal medicines to treat depression led to improvements in the condition. Recently, certain therapeutic herbs have demonstrated the same antidepressant-like properties. Some herbal medications are a few that are listed below and can be utilized to treat depression. These medications have the same psychopharmacological effects against the nervous system as antidepressants, and they help in maintaining the serotonin, dopamine, and noradrenaline reuptake, while additionally assisting in the MAO limitation and shifting of the neuroendocrine system's functions along with Hypothalamic-Pituitary-Adrenal (HPA) axis[19].

8. Flavonoids-Rich Plant with Antianxiety and Antidepressant Properties

8.1 St. John's Wort

Another name for *Hypericum perforatum* is St. John's wort. According to the current research, St. John's wort's medicinal form consists of a variety of leaves and flowering tops that contain flavonoids, which include phloroglucinols (hyperforin), xanthones, naphthodianthrones, and hypericin. Recent studies have demonstrated that *H. perforatum* has similar antidepressant effects to those of tricyclic antidepressants and selective reuptake inhibitors of serotonin[20]. *H. perforatum* has been shown to elevate the level of different monoamines and 5HT in the cerebellum, amygdala, hippocampus, and prefrontal cortex by inhibiting monoamine neurotransmitters like a substance called (5-HT), noradrenaline, and dopamine levels[21]. One of the main purposes of *H. perforatum* is overexpression of the 5-HT receptors, which has the effect of upregulating the neurons, it in turn results in a dopamine-related component lowering the neurons' background activity. This herb has effects similar to SSRIs in that it increases the element in 5-HTAA receptors. It also has effects similar to SSRIs in that it blocks GABA3 binding, which affects the central nervous system's reduced memory. *H. perforatum* has an impact on N-methyl-D-aspartate receptors (NMDARs), which are necessary for nootropics to work[22].

8.2 Lavender

Lavandula angustifolia is the scientific name for the herbaceous plant known as lavender. According to recent research, lavender has outstanding hypnotic and mild sedative effects when used in aromatherapy, and it has helped postpartum depressive disorder in women who have given birth. Recent research has shown that the active elements of lavender, linalool, and linalyl acetate quickly reach their plasma peak levels[23]. Lavender flowers contain 1-3 % essential oil, coumarin derivatives (umbelliferon, herniarin), flavonoids, traces of sterols (cholesterol, campesterol, stigmasterol, and -sitosterol), traces of triterpenes (micrometric acid, ursolic acid), up to 13% tannins, and phenol carboxylic acids (such as rosmarinic acid, ferulic acid, is feral[24]. Aromatherapy has been shown to make up most of lavender's medicinal uses, and studies have shown that the herb's effects on sleep-related breathing have enhanced sleep quality by suppressing the cause of sleeplessness. Studies have even found that an elevated 2nd phase of sleep has a substantial impact. Whereas there were no side effects recorded and sleep could be effectively induced along with an improvement in mood, this indirectly improved depression by modifying the circadian rhythm[25].

8.3 Ginseng

Ginseng is commonly managed clinically under the botanical name *Panax ginseng*. It was once considered to be one of the greatest medicines, and recent studies have proved that ginseng's component ginsenosides exhibits antidepressant-like effects in preclinical animal models. Numerous causes might cause depression, such as glial cell aggregation and blocking neuronal cells, but current research has revealed that glial cells also contain astrocytes, which are crucial to the pathology of depression[26]. Ginseng successfully controls the immune response reaction, and it also aids in the preservation of the body system. It has a variety of impacts in treating disorders that are like depression in addition to psychiatric illnesses. Recent research has demonstrated that ginseng is effective in treating the HPA axis and managing the hormones that are necessary for the subsequent phase. The HPA axis, the brain's control centre, is where cortisol is primarily made and controlled. the sympathetic nervous system also plays a vital role in this cycle[27].

8.4 Lemon balm

Melissa officinalis, usually referred to as lemon balm, is an old remedy that has long been used for treatment. *M. officinalis* has a strong antioxidant property and a high phenolic content. Lemon balm has even been shown to have immune-suppressant and antioxidant characteristics, as well as the ability to oxidize linoleic acid via autoxidation and EDTA-mediated oxidation[28]. Because of the rush of free radicals in the postsynaptic junction and its well-known antioxidant action, lemon balm has a major impact on the neurotransmitter. A recent study in Iranian diabetic patients revealed that the prevalence of depression and anxiety in diabetes mellitus patients was estimated to be 24/4% and 64/5%, respectively[29]. The appearance of depression in diabetic patients is associated with poorer medication adherence. Numerous pathways describe the applications of lemon balm and variations in the Similar amounts of serotonin (5-HT) present in the central nervous system. The antioxidant property tested targeted serotonin in the CNS[30].

8.5 *Aegle marmelos*

In *Aegle marmelos* various studies have shown the presence of flavonoids in phytochemical screening which are responsible for the anxiolytic effect through benzodiazepine receptors. Therefore, flavonoids present in *Aegle marmelos* may be responsible for the anti–anxiety activity. Various studies on *Aegle marmelos* have shown the presence of phytoconstituents other than flavonoids like tannic acid, phenols, marmesinin, ascorbic acid, eugenol, skimmianine, saponin etc., which may possess anxiolytic properties. *Aegle marmelos* can be a safe and effective drug for the treatment of several anxiety disorders. The fruit contains ethanolic extracts. These are used to care for fatigue, anxiety, and depression. The fruit has steroids, coumarin, and alkaloids[31].

8.6 *Acoros calamus*

Due to the presence of alpha- or beta-asarone, chewing the rootstock of the *Acorus calamus* herbs might result in hallucinations. In rats, the Acorus calamus exhibits neuroprotective properties against chemically induced neurodegeneration and stroke. It protects against neurotoxicity brought on by acrylamide. *Acorus calamus* leaves and roots both exhibit antioxidant qualities. Since ancient times, the Indian system of conventional healing has recognized the roots and rhizomes of the *Acorus calamus* as rejuvenating agents for the brain and neurological system. Alpha and beta asarone, two compounds found in the rhizomes of the *Acorus calamus*, have a variety of pharmacological properties, including sedative, CNS depressive, behaviour-modifying, epilepsy, acetylcholinesterase restricting, and memory-improving effects[32].

8.7 *Viola odorata*

Viola odorata, a species of the genus Viola that is native to Europe and Asia, has also made its way to North America and Tasman. It is also known by the names sweet violet, English violet, garden violet, and wood violet[33]. This flower's pleasant aroma has been well-liked throughout history, especially in the late Victoria era, and as a result, it is utilized to make numerous medical perfumes and perfumes[33]. It has been used in the conventional system to treat anxiety[34], and sleeplessness, and to reduce blood pressure[35]. Violet is mostly utilized as a natural treatment for a variety of respiratory conditions. Treatment of sore throat, coughing, and congestion can all benefit greatly from it. Recent research has revealed that Common Violet leaves contain salicylic acid glycoside, which explains why they are effective in treating headaches and other bodily ailments. Common violet flower syrup possesses expectorant, laxative, anti-inflammatory, and antiseptic qualities. In addition to treating headaches, sleeplessness, vertigo, and tiredness, it can be beneficial in cases of certain respiratory disorders, Alkaloids, glycosides, saponins, methyl salicylate, mucilage, and vitamins E and C are all present in the viola[36]. Along with other therapeutic effects, the plant has been claimed to have anti-inflammatory and diuretic properties, but no research has been identified on its ability to decrease cholesterol or blood pressure[36].

9. Polyphenols: Antianxiety and Antidepressant Activities

Because oxidative stress and anxiety have been connected, we undertook a study to investigate the effect of an antioxidant on mental strain[37,38]. We choose chlorine dioxide as the antioxidant model since it is one of many common polyphenols consumed by humans and may be in large quantities in fruits such as apples, plums, and berries (Table 1). We discovered that the chemical chlorogenic acid significantly decreased anxiety in mice without impairing their ability to move[37]. The curve of dose-response for chlorogenic acid appeared to have a reverse U-shape in the light/dark choice test: 20 mg/kg were productive, while 3, 13, and 65 mg/kg were not[37]. The hypothesis that the medication acts on multiple organs (stimulant, depressive), each of having distinct criteria for sensitivity, is commonly used to explain the distribution of doses in psychopharmacology. We established the active chlorogenic acid dosage's anxiolytic-like effects in the elevated plus maze[37]. The anti-anxiety effects of chlorogenic acid were abolished when flumazenil, a benzodiazepine receptor antagonist, was combined with it (20 mg/kg, intraperitoneal injection). This finding indicated that chlorogenic acid acts as a benzodiazepine receptor agonist to reduce anxiety in mice[38]. This outcome appears to refute our initial theory that chlorogenic acid's ability to act as an antioxidant accounts for its ability to reduce anxiety. Nevertheless, we concluded that chlorogenic acid has two favourable effects that may help worried subjects: cytoprotective and anxiolytic effects[39]. Chlorogenic acid is proven to be digested in the small intestine without causing any structural changes[40]. This raises the polyphenol's nutritional value and implies that fruit consumption, including that of apples, plums, cherries, and other fruits, should be encouraged. Our results support those who showed that polyphenols might interact with the GABAA transmitter[40]. These researchers discovered that the neuroprotective compound EGCG (Table 1), a polyphenol present in green tea, can be utilized to

Table 1. Dietary polyphenols: anxiolytic-like effects, antidepressant-like effects, side effects and dietary sources

Polyphenols	CNS Activity	Adverse event	Dietary Source
Chlorogenic acid	Sedative effects[42]		Fruits and vegetables of many varieties (apples, plums, cherries, etc.)[43,44].
Rosmarinic acid	Anxiolytic-like and antidepressant-like actions[45]		Peel of apples[81].
Caffeic acid	Antidepressant-like effects[45]		Several different kinds of vegetables and fruits (apples, plums, cherries, kiwi fruit etc.)[43,44].
Quercetin	Anxiolytic-like effects[47]	Sedative effect[48].	Different types of natural products (apples, plums, onions, broccoli, tea)[43,44].
Rutin	Antidepressant-like effects[46]		Different types of natural products (apples, plums, cherries, onions, tomato, etc)[43,44].
Apigenin	Anxiolytic-like effects[48]	Slight sedative effect[48]	Parsley and celery[48]

lessen anxiety[41]. Additionally, some naturally occurring flavonoids, such as apigenin (Table 1), have a specific and comparatively low activity for benzodiazepine receptors. The pharmacological profile of these compounds points to a limited agonistic action that might induce the anxiolytic-like benefits of polyphenols without the negative side effects. Apigenin causes no depression or myorelaxant effects in mice when administered at 3 mg/kg. However, a tenfold rise in the flavonoid dosage led to very little sedative effects[41]. Rosmarinic acid is another example of a polyphenol that lessens anxiety at lower levels (Table 1).

10. Phytoflavonoids and the Monoaminergic System

According to the monoamine theory of depression, a drop in the levels of the catecholamine NE and the indoleamine 5-HT in the synaptic cleft is related to anxiety and depression. These substances' serotonergic properties provide them with anxiolytic and antidepressant effects. Metabolic abnormalities of monoamine neurotransmitters implicated in NE, 5-HT, and DA signalling are the primary molecular causes of depression. Additionally, it was discovered that the HPA axis's ability to function properly was impaired in many depressive patients. Numerous flavonoids have been found to have anti-inflammatory, antioxidant, and antidepressant properties in animal studies[49].

11. Phytochemicals are used Against Anxiety and Depression

11.1 L-theanine

The plant *C. sinensis*, also known as green tea, is the source of the amino acid L-theanine. In contrast, L-theanine has the amazing ability to cross the blood-brain barrier and has been demonstrated to increase brain volume in a dose-dependent manner. Numerous preclinical research on rats studied the loss of hippocampal CA1 over time following stimulation to the stressful suppression of recall of recognition. L-theanine and its antidepressant abilities were found to be more helpful in treating cognitive impairment in mice. L-theanine exhibits agonist action when combined with NMDARs to treat depression. L-theanine has demonstrated superior efficacy in the treatment of stress and phobia in healthy volunteers. It has been demonstrated that L-theanine sympathetically reduces nerve responses[50]. Numerous investigations have demonstrated that prefrontal cortisol function, which has a dominant impact on cognitive impairment and processes related to memory impairment, has an impact on both sites and -waves of electroencephalogram[51].

11.2 Carvacrol

Oregano and thyme are combined to produce the fragrant herb carvacrol. Essential oils and aromatic plants both contain a significant amount of carvacrol. It has proven to have a variety of cognitive benefits and a considerable effect on depression. Even though the safety index has not been determined, it has been established that the substance is a chemical flavonoid. Because carvacrol only affects depression in females during the oestrous cycle and because it has been demonstrated to affect the serotonin and metabolites tissue composition of the prefrontal cortex, cerebellum, and nucleus acumens, it has been the subject of numerous clinical studies[52]. The monoterpenoid phenol carvacrol significantly affects the V3 and A1 potential, which is what causes the warmth. Carvacrol modulates human ion channels and transient receptor prospective in turn. Carvacrol has the important feature of inhibiting the depression caused by cyclooxygenase-2 and functioning on the peroxisome proliferator-activated receptor[53,54]. Administration of carvacrol has been shown to affect dopaminergic brain circuits, increase levels of 5-HT and dopamine, and stimulate the prefrontal cortex[55].

11.3 Curcumin

Curcumin comes from turmeric, also called *Curcuma longa*. These phytoconstituents have shown that the levels of neurotransmitters in the brain are enhanced where it has an antidepressant action and is prevented by MAO B and A. The depressing characteristics of curcumin have been proven to represent the cytokine explanation and the monoamine hypothesis, which together make up the primary hypothesis of depression[56]. Whereas curcumin has demonstrated an elevation similar to that of tricyclic antidepressants in the amount of monoamine that can attach to the binding site[57]. Curcumin has been shown to exhibit anti-inflammatory activity, which supports the cytokine hypothesis that these molecules play a vital part in the emergence of the main depressive problem, according to the mechanism. Additionally, curcumin has shown a significant inhibitory effect on the anti-inflammatory cytokines nuclear factor kappa A, NLRP2 inflammatory mediators, and interleukin-2A. Trials with curcumin from a long time ago coupled with conventional therapy have shown it to be neuroprotective[58]. Furthermore, behavioural modifications in the Brain-Attached Neurotrophic Function (BDNF) and HPA axis have been demonstrated in laboratory investigations. It was discovered that treating synthetic medicine alongside a natural plant or phytochemical was an innovative approach to the medical profession[59]. The investigation employed a lot of the drug curcumin, and the action was discovered to be synergistic. The HPA axis and the disrupted monoaminergic pathways may be brought into balance by large-scale sequential therapy options for depression[60].

11.4 Ferulic Acid

The organic substance ferulic acid is mostly present in plant cell walls, seeds, and leaves. According to reports, ferulic acid has a variety of neurotherapeutic actions that include reducing apoptosis, high levels of Reactive Oxygen Species (ROS), and glutamate excitotoxicity[61]. The aberrant increase in indoleamine 2,3-dioxygenase activity in the brain is what leads to the abnormal switch in tryptophan metabolism away from serotonin. Where ferulic acid has proven to have antidepressant properties, the fall in cerebral levels explains the efficiency of medicines and must be boosted[62]. The main study discovered that depressive persons typically exhibited the effects of reduced and hyperactivated NMDAR, which causes cell death, and excess glucocorticoid synthesis, which is involved in antioxidant defence. The majority of therapies for treating depression will be monoaminergic systems[63].

11.5 Proanthocyanidin

Apple, cocoa, beans, grapes, tea, and other plants also contain proanthocyanidin, an oligomeric and molecular flavan-3-ol[64]. Proanthocyanidin can counteract the increased levels of mediators of inflammation in the prefrontal cortex of the brain and amygdala, according to research[65]. Together with peroxidase, superoxide dismutase, and catalase enzymes, proanthocyanidin is a protective substance that functions as an antioxidant and aids in the reduction of glutathione in the liver[66]. Where proanthocyanidin maintains ROS scavenging activity and has a natural antioxidant function. In comparison to the antioxidant vitamins C and vitamin E, proanthocyanidin has demonstrated improved hydroxyl radical scavenging[67].

11.6 Resveratrol

Red wine and grapes both contain the natural phenol known as resveratrol. Resveratrol exhibits exceptional neuroprotective qualities[68]. By reducing the excitability of the HPA axis, resveratrol has a substantial impact on the control of the anxiolytics effect. Resveratrol is also implicated in the breakdown of adrenaline and dopamine and functions as a further anxiolytic function. The most common method of demonstrating resveratrol's impact is by the control of BDNF in the brain. Resveratrol has been demonstrated to have a predominant role in functioning as a neuroprotective ingredient with a significant capacity to increase neurogenesis, alongside many other brain problems. The finest sleep inducer having anti-ageing characteristics has also been demonstrated to be resveratrol[69]. The hypothalamic-pituitary-thyroid centre and the HPA axis are both affected by depression, which is also associated with monoaminergic and molecular markers. Resveratrol has been shown in numerous studies to operate on 5-HT and adrenaline to regain the monoaminergic system's normal function and to induce an anxiolytic effect through BDNF-work transcription in the body[70].

12. Other Essential Flavonoids Act as Anti-anxietic Agents and Antidepressant Actions

12.1 Apigenin

Fruits and vegetables include an antioxidant called apigenin, a 4´, 5, 7-trihydroxy flavone. Numerous medical effects have been documented, including antineoplastic, analgesic, and antioxidant properties. Apigenin has been shown to have anxiolytic properties in several pre-clinical investigations. Nakazawa evaluated the antianxiety effects of apigenin via a forced swim experiment on rodents and found that it enhanced resistance-like behavior in animals, which was supported by the cholinergic pathway[71]. In a different investigation, mice treated with an unexpected chronic mouse model were used to evaluate whether apigenin had an antidepressant effect. The analysis of the researcher suggests that two increases in the level of expression of the Peroxisome Proliferator-Activated Receptor (PPAR), which blocked the production of NLRP2 and ILL, may be the source of the action[72]. Apigenin's ability to increase hippocampal BDNF levels and block the mono-amino oxidase enzyme is more evidence of its antidepressant effects, because it can decrease inflammation[73] (Figure 3).

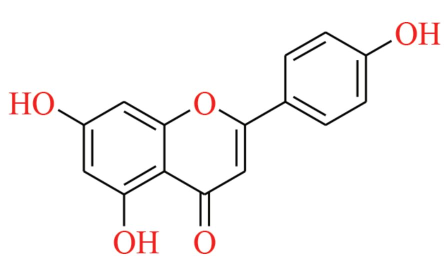

Figure 3. Apigenin.

12.2 Baicalein

Baicalein is a trihydroxyflavone flavonoid that contains hydroxyl molecules at positions 5, 6, and 7. Baicalensis has been shown to contain the most active flavonoid. According to multiple reports[74], baicalein is a powerful chemical with properties like many others, including antioxidant and free radical scavenging action. This flavone passes the blood-brain barrier and notably exhibits relaxing and CNS depressive effects, according to published research[75]. Additional studies have shown that baicalein, which was isolated from the root of the Scutellaria plant using ethanolic extraction, could inhibit the brain, contribute to a drop in prostaglandin E2 amounts in the brain, act as a strong antioxidant, and stop the emergence of depressive behaviour in mice models. Six out of 48 rodent brains were reported to have lower prostaglandin E2 levels. Additionally acting as a strong antioxidant, this chemical helps to manage mice's chronic stress behavior[76] (Figure 4).

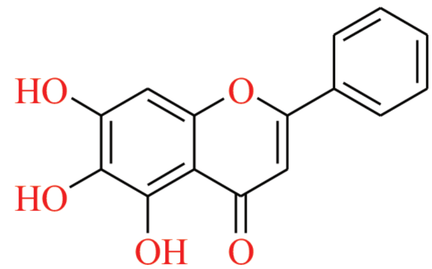

Figure 4. Baicalein.

12.3 Myricetin

Myricetin, a hexahydroxy flavone, has hydroxyl groups replaced at positions 3, 3′, 4′, 5, 5′, and 7. Vegetables, dry fruits, rum, tea, and other substances are all widely available. It has been proven to have analgesic, anti-cancer, and anti-depressant effects[77]. In a study, it was found that myricetin inhibited the FST-predicted depressive behaviour in stressed-out mice. Myricetin's anti-depressant potential was increased by research showing that this flavonol reduced blood levels of corticosterone, elevated BNF levels, and increased oxygen species reactive enzyme production in the brain[78] (Figure 5).

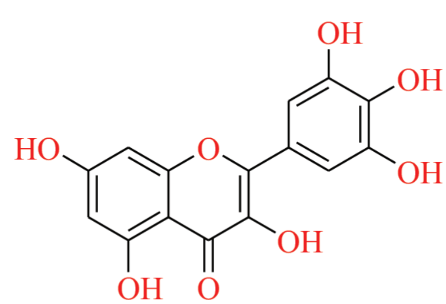

Figure 5. Myrecetin.

12.4 Quercetin

Quercetin, also known as pentahydroxy flavone, is often found in pineapple, garlic, ginger, and red wine[79]. Numerous flavonoids exhibit strong anti-free radical capabilities that can be used to treat a range of diseases and conditions[79]. In a few animal models, the anxiolytic function was also proven, and it was found that MAO inhibitors raised the levels of 5HT and nor-epinephrine in clefts of synapses. According to research showing quercetin's antidepressant effects in diabetic animals, it may be utilized as a preventative measure to reduce stress in diabetes conditions[80] (Figure 6).

12.5 Rutin

Citrus bioflavonoids like rutin (tetrahydroxy flavone), also known as sophorin, quercetin, and rutosine, are also known by these names. This is a glycoside composed of the flavonoid myricetin and the saccharide, with

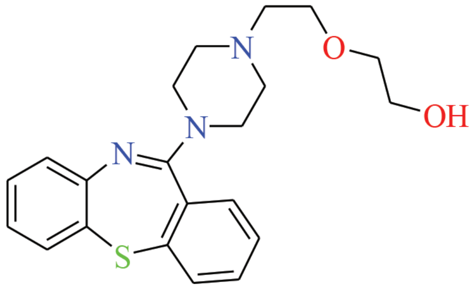

Figure 6. Baicalein.

the sugar groups rhamnose and glucose substituting for the -OH group of the quercetin at position C3. Citrus-containing foods, plants, and beverages have all been discovered to contain, including figs, wheat, tea made from green tea, and others[81,82]. It facilitates collagen synthesis and vitamin C absorption by the body. Numerous activities of rutin, including neural protection, antioxidant properties, analgesic effects, and anti-tumour characteristics, have been reported[76]. Through the methanolic extract of *Schinus moll* L. and its aerial parts, a substance separates that exhibit CNS suppressive effects in TST. Increases in the level of rutin anti-depressant substances were evidence for their effectiveness of 5HT and noradrenaline[83] (Figure 7).

13. Conclusion

Potent naturally occurring antioxidant compounds known as polyphenols have been shown to have pharmacological effects on the Central Nervous System (CNS). Given the effects benzodiazepines, which are full agonists, have adverse effects like reliance, polyphenols with partial agonistic characteristics at the receptor site may be attractive anxiolytic medicines. It may be possible to successfully reduce the active dose while also facilitating the passage of polyphenols over the blood-brain barrier by administering them intranasally in the form of liposomes. Certain polyphenols can be used to treat depressive people by regulating their emotions because they have been shown to have similar advantages to traditional antidepressants at lower doses. The emergence of anxiety, depression, and other diseases linked to oxidative stress may be prevented (or delayed) with a varied diet rich in naturally occurring polyphenols.

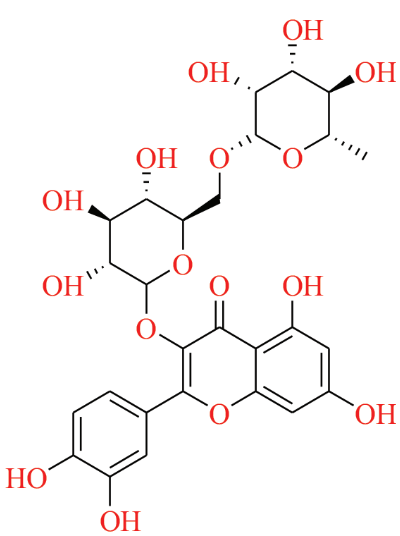

Figure 7. Rutin.

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