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SHORT REVIEW

The Challenging Role of Flavonoids as a Potential Phytochemical to Treat Anxiety

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Abstract

Numerous mental diseases can be caused by anxiety or anxiety-like effects, but phobia is a prevalent overcoming symptom that frequently causes stress. At present, two primary anxiety-treatment approaches are being considered: Psychotherapy and pharmacotherapy. So many traditional synthetic anxiolytic drugs with such a variety of side effects are used in the pharmacological clinical approach. As a result, scientists are searching for studies that will help them find suitable safe medications from plant sources. large experimental studies have assured that dietary phytoconstituents such as terpenoids, alkaloids, phenolic compounds, flavonoids, lignan, saponins, and cinnamates, and plant infusion comprising a combination of the various substance, have stronger action in a variety of the anxiety models in animals. The mechanisms of action of anxiolytics involve relationships with the GABA A receptor on both non-BZD sites and in Benzodiazepine (BZD).

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

1. Introduction

Anxiety condition is the most familiar type of maniac disorder in the United States and several different countries and its parts. Anxiety disorders are classified by the Diagnostic and Statistical Manual of mental disorder (DSM) American Psychiatric Association, 2001, anxiety disorder includes panic attack, apprehension, post-traumatic maniac condition, anxiety condition, expanded, stress about social conditions, Compulsive Behavior Disorder (OCD) expressed by invasive, and avoid potential[1].

Anxiety disorders are linked to serious disability rates of chronic conditions, and elevated numbers of comorbid conditions for identical intersect for a wide range of brain disorders (mood problems). We begin this review article with a short description of neurofunction and the neurological parameters of anxiety and fear using the most recent transcriptional models[1]. Then, we look at some of the newest promising ways in neurochemistry anxiety investigation, with a special focus on transcriptional findings related to the creation of new therapies. Anxiety is a harmonic situation of emotional stimuli that include feelings of fear or worry. Patients with worry, as opposed to patients with fear, frequently understand danger sources only vaguely. Anxiety is the most common behavioral problem, according to studies, and studying factors that affect students' anxiety reveals that physiological features, items relating to growth phases, and social, relatives, and factors all have a major impact on anxiety. Anxiety disorder affects approximately 500 million people worldwide[2]. Anxiety manifests itself in a variety of mental and physical symptoms, such as increased heart rate, stomach cramps, perspiration, bronchitis, motion sickness, tired, urination, a condition of apprehension and anxiety, failure to meet a role, doubt about the future, the anticipation of a sad event, inability to concentrate, poor sleep[3].

2. Neuroanatomy of Fear and Anxiety

Amygdala is a primary brain part responsible for the passing of frightening material, as it relays the immediate threat response by incorporating knowledge from sensory properties, relevance, and previous knowledge using

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subcortical and cortical inputs[4]. Sensory input attains the central nervous system via the frontal thalamus in the organism's fear response, imploring the amygdala to start physiological and neurogenic reactions through forecasts by the cortex and brain tissue nuclei portion. Fear, a comparatively short, sensory reaction, and anxiousness, a more prolonged reaction stimulated by situations of unpredictable hazard, have distinct amygdala pathways in rats[5]. The old pathway involves the amygdala's basolateral, central, and medial nuclei, whereas the latter includes forecasts from the dorsal motor amygdala to the stria terminals bed nucleus. According to a meta-analysis of neuroscience, scared stimuli especially activate the stress response in healthy human participants, which is consistent with animal literature[6]. According to human neurocircuitry models, amygdala action is enhanced by top oversight of the medial prefrontal portion such as the orbitofrontal part, and through the midbrain, permits relevant pieces of information like a sense, accurate memory characterizations, and consciousness to promote danger-restoring. amygdala and frontal cortex have a mutual relation and are also involved in a near-extinction mode[7]. A distinctive pattern of enhanced amygdala reactions to threat signals has been recorded in a variety of anxiety disorders and can be witnessed in the very initial stages of analysis, such as when a masked trigger design precludes awareness of stimulation[8].

3. Currently Marketed Drugs for the Management of Anxiety Disorders

Therapies and pharmacologic options Historically, Tricyclic Antidepressants (TCAs) were used. There are various treatment options for anxiety disorders, such as Cognitive behavioral treatment, that have uses broadly utilized for the rehabilitation of patients and have shown comparable capabilities to SSRIs for severe anxiety and

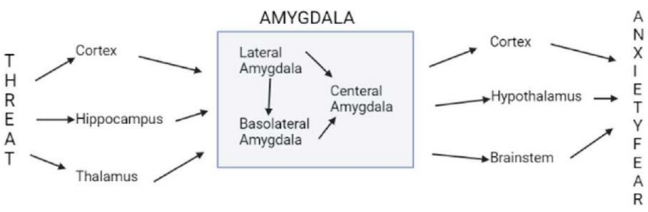

Figure 1. Neuroanatomy of fear and anxiety.

Generalized Anxiety Disorder (GAD). TCAs, on the other hand, have small tolerable adverse effect benefits and safety problems (including objectionable anticholinesterase and cholinergic effects), as do Mao inhibitors (adverse results involve sleeplessness, hypnotics, low bp, sexual problems, episodes of mania, weight acquire, hypertensive episode, and tonic-clonic jerking)[9]. Serotonin reuptake inhibitors (e.g., venlafaxine, phenelzine, Zoloft) are first-line therapeutical agents for all mental illnesses, with proof from multiple, randomized, non - randomized experiments that lead to their own activity and safety. Serotonin-norepinephrine reuptake inhibitors (for example, duloxetine) also becoming primary treatments for stress and depression, most notably generalized anxiety. SNRIs and SSRIs inhibit serotonin and noradrenaline reuptake after discharge from the brain, properly, increasing their availability at the synaptic cleft, neurotransmission efficacy, and resultant effect in another neurotransmission[9]. paroxetine's slower therapeutic onset (2 to four weeks) relates to subtle improvements in brain function and structure. Animal studies have shown that SSRIs' behavioral effects are aided by the development of new cells within the hippocampus. while changes in mobility may be the possible mode that these drugs help counter hyper effects to pressure in depression and anxiety[10].

3.1 Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors (SSRIs and SNRIs)

The first-line use of paroxetine (SSRIs) and duloxetine (SNRIs) is advised due to their superior benefit/risk balance. Patients should be made aware that these antidepressants start working their anxiolytic effects 1 to 3 weeks after taking them (up to 6 weeks). The negative effects could be more pronounced for the first two weeks. There may be acute muscle twitching or a rise in negative symptoms, which could make it harder for patients to adhere to their treatment regimens. These negative effects could be lessened by decreasing the antidepressant's initiating dosage. According to a review of research done on depressed patients, SNRIs may not be as well tolerated as SSRIs[11].

Yet, medical condition suggests that desirability varies and that a specific patient could lower side effects when switching between an SSRI and an SNRI.

Table 1. List of medications currently used in the management of anxiety along with their MOA and AE

Class of medication	Examples	MOA	Adverse Effects
SSRIs	Citalopram Escitalopram fluvoxamine Paroxetine Sertraline Duloxetine Fluoxetine	5HT reuptake is selectively inhibited.	Nervousness, nausea, impatience, diarrhoea, bowel problems, tiredness, vomiting, blurred vision.
SNRIs	Venlafaxine Duloxetine	By blocking neuronal reuptake of 5-HT and NE, it improves monoaminergic function.	Nervousness, nausea, impatience, headache, tiredness, tremors, libido problems, stomach pain, appetide change, nephritis.
tricyclic antidepressant	Clomipramine	Blocking the NET and SERT inhibits 5-HT and NE reuptake.	Side effects include pharmacological effects, somnolence, blurry vision, CVS problems, weight loss, glare in eyes, loss of libido, vomiting.
Calcium modulator	Pregabalin	Pregabalin, a novel mode of action (MOA) compound, has shown efficacy as an adjuvant therapy epilepsy medication in several neuropathic pain models. Pregabalin has the same efficacy as benzodiazepines and venlafaxine in several studies for generalized anxiety disorder (GAD).	Dizziness, somnolence, sore throat, edema, loss of vision, weight gain, bowel problems, euphoria, balance disorder, reduced appetite, difficulty concentrating/attention, or other side effects.
5-HT1A agonist	Buspirone	5-HT1A receptor selective agonist.	Dizziness, vomiting, sleeping problems, nervousness, chest pain, and other symptoms may occur.
a2-antagonist	Mirtazapine	Presynaptic a2-receptor improves monoaminergic function by disinhibiting 5-HT and NE release.	Agitation, mental confusion, fever, migraine, loss of coordination.

Just because a few SSRIs and SNRIs are cytochrome P450 enzyme inhibitors, they may communicate with other psychostimulant medications and treatments for medical illness[11]. Withdrawal symptoms can occur after discontinuing SSRI treatment. However, such is much less severe and common than the symptoms of withdrawal seen after discontinuing benzodiazepine therapies. These side effects could be highly common in relation to citalopram other than with mirtazapine.[12]

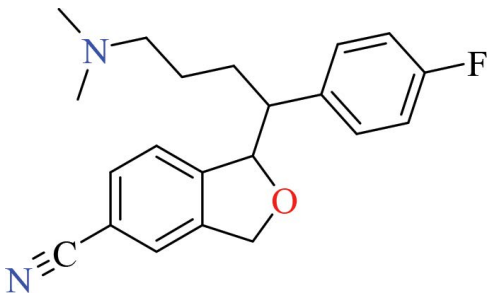

Figure 2. Citalopram.

3.2 Calcium Modulator

Pregabalin is just a calcium mediator medication that works by binding to the subunits of the calcium-gated channel. The calcium modulator has sedative effects. Sleep problems, that are prevalent in anxiety disorder groups, may improve sooner by pregabalin than if it is related to SSRIs. Pregabalin has a quicker onset of efficacy than antidepressant medications. Pregabalin does not undergo renal biotransformation and therefore does not relate to cytochrome P450 enzyme stimulators. However,

there have been reports of pregabalin abuse in people that suffer from drug addiction and detachment etiologies after abrupt discontinuation[13].

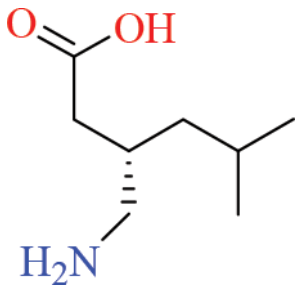

Figure 3. Pregabalin.

3.3 Tricyclic Antidepressants

Conventional pharmacological interventions (TCAs) clomipramine and imipramine are just as efficient as 2nd antidepressant medications in anxiety disorder treatment. TCAs have a higher rate of adverse reactions than SSRIs or SNRIs. As a result, such treatments must be attempted before TCAs are used. The amount should be steadily increased until it reaches the levels utilized in depression treatment. TCAs should be utilized with caution in individuals who are recognized as suicidal because of their possibly fatal toxicity within a week of overdose[14].

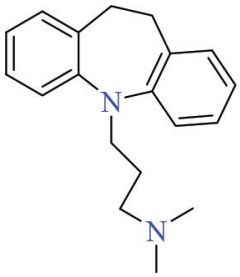

Figure 4. Imipramin.

3.4 Serotonin Receptor Agonist

Buspirone, a serotonin receptor 1A (5-HT1A) agonist, is effective in the management of anxiety in some controlled studies. Not all the protocols, however, demonstrated dominance to control and/or comparability to marketed drugs[14].

3.5 Benzodiazepines

Benzodiazepines sedative effects start shortly within a week of oral or parenteral administration. Benzodiazepines,

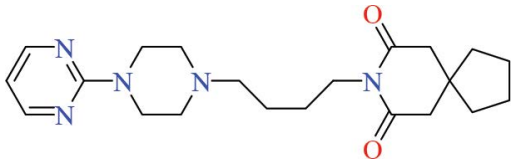

Figure 5. Buspiron.

except antidepressants, do not cause higher jitteriness and insomnia at first. In the U.S. benzodiazepines are used to treat 56% to 95% of patients who suffer from anxiety. like, many studies have shown a high chance of benzodiazepine need However, benzodiazepine usage is attached to central and peripheral system (CNS) anxiety, which can cause fatigue, drowsiness, enhanced reflexes, impaired vision abilities, and other unwanted effects. memory functions, particularly in the elderly, may be impaired. Long-term benzodiazepine treatment (e.g., 4 to 8 months) may result in dependency in some patients, particularly in individuals naturally inclined to substance abuse[15]. Tolerance (characterized by an individual's steady thought to select the right dose) appears too uncommon. As a result, before beginning benzodiazepine treatment, the risks and advantages should be carefully considered. Benzodiazepines were not preferred as first-line treatments according to the current guidelines. The direction to use newer antidepressants depends on the well-known risks of benzodiazepines rather than direct comparative studies[16].

3.6 Mao Inhibitor

Moclobemide is a monoamine oxidase inhibitor that is both selective and reversible. It is used to treat seasonal affective disorder. Because none of the studies have found the drug to be superior to a placebo, it is not suggested as a primary diagnosis[16].

3.7 Antidepressant

The antidepressant medicine agomelatine, which behaves like a ligand for MT1 melatonin neurons as well as an opponent for the serotonin 5-HT3C target, is shown to be useful[17]. Even so, the drug is only approved to treat major depression, not GAD. Withdrawal signs and sexual problems are less likely with agomelatine even than with Selective serotonin reuptake or SNRI antidepressant medications. Hepatic enzyme elevations occur in approximately 14% of treated patients[18].

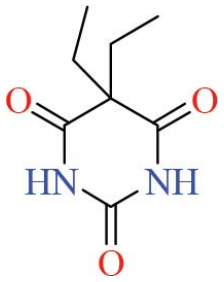

Figure 6. Barbital.

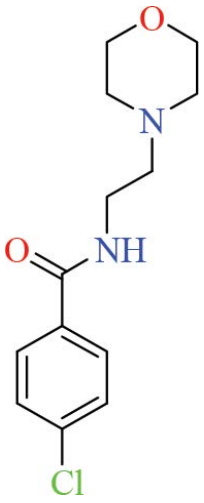

Figure 7. Moclobimide.

3.8 Antipsychotic

A few studies on Generalized Anxiety Disorder (GAD) have shown that the antipsychotic drug quetiapine is efficient. It is typically prescribed in doses ranging from 150 to 600 mg/day for therapies for schizophrenic psychoses. A smaller dose of (40 to 350 mg/day) is essential to treat anxiety. Nowadays, most countries did not approve of the drug for anxiety disorders, most likely because of side effects like metabolic syndrome. In general, patients who received lower doses experienced fewer classic side effects, like sedatives or weight gain. Only in treatment-refractory patients can drugs be used off-label. Efficacy begins sooner than with antidepressants[19].

4. Phytotherapy

Several observational trials have shown that an oral administration of lavender oil can help in GAD and combined anxiety[20], still is unknown as to if the lavender

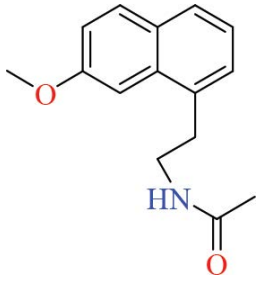

Figure 8. Agomelatine.

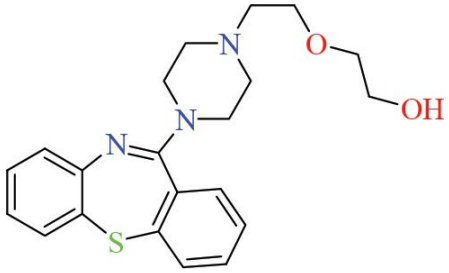

Figure 9. Quetiapine.

extract is good as standard medication The relational experiments used small concentrations of the rivals, such as 20 mg fluoxetine in a day for day 50 and a single tablet of diazepam 1.5 mg in a day 69, which may cause resulted in the rival drugs being ineffective. Kava (Piper methysticum) studies yielded inconclusive outputs[21], and the decoction was taken out from sale from certain places by its hepatic injury in different formulations. the non-API controlled studies of depressed groups, Valerian extract is ineffective[22]. John's wort was not also successful in generalized anxiety disorder. different phototherapeutic was studied for groups of people with anxiety disorders. The proof for the examined products is insufficient because of the low standard of these studies. In herbal preparations, standardization may be a problem. It was discovered, for example, the material of the putatively efficient ingredients varied significantly between various plans of St. John's wort[23].

5. Flavonoids-Rich Plants with Anti-Anxiety Properties (Table 2)

5.1 *Aegle marmelos*

Aegle marmelos also referred to as bail (or bili or bhel), is a unique tree variety belonging to the Indian part and Southeast Asia. It is also known as Bengal quince, Japanese

tangerine juice, stone apple, or wood apple. It is found in the nations of India, Nepal, Sri Lanka, and Burma. Several studies on *Aegle marmelos* have shown that flavonoids are present in phytochemical analysis, which is liable for the anxiolytic impact via benzodiazepine receptors. As a result of the antianxiety and anti-depressants, the activities of *Aegle marmelos* are potentially due to flavanols. Other than flavonoid, numerous reports on *Aegle marmelos* have revealed the presence of phytocompounds such as tannins, quinones, marmesin, ascorbic, skimmianine, saponin, and eugenol, among others, which results in antianxiety effects. *Aegle marmelos* can be an effective and secure treatment meant for a variety of anxiety disorders. Ethanolic extracts are present in the fruit. These are prescribed to treat tiredness, anxiety, and depressed mood. Glucocorticoids, coumarin, and alkaloids are found in the fruit[24].

5.2 *Rauwolfia serpentina*

Rauwolfia serpentina, also known as Indian snakeroot, devil pepper, as well as serpentine wood, is a milkweed flower in the Apocynaceae family. Its native range includes the Indian subcontinent and Asia (from Indonesia to India). The root of Rauwolfia is used to treat high BP and insanity in humans. also used to manage nervous system problems like stress and phobia. The use of serpentine to treat sleep patterns, brain illnesses, and rude behavior. It soothes anxiety condition and decreases stress and aggression behaviour. It has the potential to treat

Table 2. Flavonoid containing antianxiety plants with other biological activities

Sr No.	Plant	Part used	Therapeutic compounds	Screened activities
1	*Aegle marmelos*	Leaves and roots	Aegeline, Coumarin, Marmeline	Immunogenic, anti-diabetic, and anti-fertility
2	*Aloysia triphylla*	Root	Flavanone (Artemisinin, Hesperidin)	anti-malarial, Antidepressant
3	*Avena sativa*	Seed	Carotene, polyphenols, antioxidants	Eczema, skin rash,
4	*Bacopa monnieri*	Root, stem, leaf	Alkaloid, brahmine, serine, triterpenoid	Sedative, antiepileptic, memory enhancer
5	*Cimicifuga Racemosa*	Roots	Actaealactone, cimicifugic acid	Kidney disorder, rheumatism, snakebites
6	*Citrus aurantium*	Flowers	Flavanone glycosides and hydroxycinnamic acids are examples of phenolic compounds.	Antidepressants, anticonvulsants, antianxiety, and antioxidants.
7	*Echium amoneum*	Leaf and buds	Gama linolenic acid, palmitic acid stearic acid.	Antihyperlipidemic, cholesterol-lowering, antimicrobial, anti-diabetic, and antioxidant.
8	*Embilica Officinalis*	Leaf, flower	Catechol, gallic acid, quercetin.	Anti-inflammatory, anti-cancer, and anti-diabetic characteristics.
9	*Lavandula angustifolia*	Flowers	Hydroxycinnamic acids and flavone glycosides are examples of phenolic compounds.	Anxiolytic, antidepressant, anticonvulsant, and antioxidant.
10	*Melissa officinalis*	Bark and leaf	Rosmarinic acid, threeterpinene, flavon glycoside, Z citral.	CVS, Antirheumatic, Antiepileptic, Anxiolytics, Antidepressant.
11	*Piper methysticum*	Leaves	Chalcones, Kavalactones.	Respiratory problems, Anticonvulsant,
12	*Rauwolfia serpentina*	Roots	Ajmaline, reserpine, serpentine	Hypertension, anxiolytics, sedative
13	*Rosmarinus officinalis*	Leaves	Cineol, camphor, linalool	Spasm, antidepressant, rheumatic pain
14	*Valeriana officinalis*	Flowers	Valerenic acid, hydroxyvalerenic acid, acetoxyvalerenic acid.	sedative, antiepileptic, analgesic, purgative, antiseptic, and antihyperlipidemic properties.
15	*Viola odorata*	Leaves and flowers	Cycloviolacin O2, eugenol, phytol, octadecanoic acid.	Antidepressants, antihyperlipidemic agents, anticholesterol agents, antineoplastic agent.

symptoms, seizure disorders, schizophrenia, and mental illnesses[24,25].

5.3 *Rosmarinus officinalis*

Salvia rosmarinus, also defined as rosemary, is a Mediterranean herbaceous plant with a good smell, natural thread leaf, and pale, purplish, or dark flowers. It was previously known as *Rosmarinus officinalis*, which is now a synonym. It associates with the Lamiaceae family of sages and consists of different other therapeutic or culinary herbs. "Rosemary" is derived from the Latin term Ros Marinus Officinalis. Rosemary's roots are fibrous. In folk medicine, Rosmarinus officinalis L. has most of the therapeutic benefits in healing or trying to manage a broad range of problems, including mania and stress. The content of *R. officinalis* had an antianxiety-like effect because it lowered, the immobility period swimming test in rodents when relate to the control. findings give that *R. Officinalis*' antidepressant result is activated by communication and by the monoaminergic pathway and the plant must be studied later as a different treatment target in the management of anxiety[26]. In recent years, rosemary diterpenes demonstrated *in vitro* and *in vivo* to restrict neuronal death caused by a variety of agents. The chemical constituents' multifunctionality is discussed, ranging from overall antioxidant and anti-neuronal preservation to other exact methods such as neuroinflammation and amyloid beta formation[27].

5.4 *Avena sativa*

Avena sativa is primarily used to treat muscle spasms and mental conditions associated with debilitation. Heart problems, uneven seminal discharge issues, and convalescent mental problems are all general signs of *Avena sativa*. (Totho Shastho) Naturopathic *Avena sativa* seems to have a selective effect on the nerves of the gastrointestinal apparatus in male function neurasthenia. Because of its ability to selectively affect the entire nervous structure that provides the reproductive organs. This remedy can easily remove nervous muscle twitches in the heart, sleeplessness, nervous problem, central condition, and overall problem caused by overdoing masturbation[27].

5.5 *Bacopa monnieri*

Bacopa monnieri is a creeping herbaceous plant origin in the ponds of India, Australia, Germany, Africa, China, and South America. Water hyssop, thyme-leafed Graciela, the rhizome of grace, and Indian pennywort are some of their common names. So many studies have shown that *Bacopa monnieri* leaf extract protects against neurodegeneration in animal models. Memory, anxiety, and brain health are all improved by the herbal remedy and extract. It's also used to treat seizures, pharmacological material, cognitive function, and improve memory function. It aids in the treatment of depression and attention-short overreact disorder. In healthy older study participants, the whole plant standardized dry extract affects brain abilities and its safety and tolerability. The study adds to the fact that it has the main to safely improving brain activity in the elderly[28].

5.6 *Emblica officinalis*

Phyllanthus emblica, also defined as myrobalan, emblic myrobalan, Indian mulberry, Malacca plant, or amla, is a deciduous tree in the family of Phyllanthaceae. It is natal to South Asia. Memory problems, psychological tiredness, stress with emotional irritability and sleeplessness, anxiety with hostile responses, and attention deficit disorder can all benefit from *Emblica officinalis*. Amla can help with the following health issues: Memory problems, mental lack of energy, and vertigo are all symptoms of brain and nerve discomfort with a burning sensation, a pain with vibrating and throbbing pain, and vertigo. Stress with mental tiredness and agitation, depressed mood with forceful reactions, insomnia, and violent mental agitation are examples of psychological diseases[29].

5.7 *Valeriana officinalis*

Valeriana is the flowering plant genus belonging to the family of Caprifoliaceae, the members of which are usually referred to as valerians. It includes many species, including *Valeriana officinalis* and garden valerian. Valerian extract can induce sedation by increasing GABA levels in the brain. Sedative neurotransmitter like GABA is important, and in a high number of concentrations, leads to sedation. Based on the findings of the in-lab study, valerian could induce inhibitory neurotransmitters to also release from brain fibers and prevent GABA, forced to return in neurons. Furthermore, Valerian's valerenic prevents the recurrence of an enzymatic activity that demolishes GABA and is yet another method that valerian could really boost GABA amounts and promote a good night's sleep. Researchers discovered that valerian origin increases the quantity of a substance in the CNS referred to as GABA. GABA

regulates nerve cells and reduces anxiety. Alprazolam and diazepam, for example, have GABA concentration increases in the brain. The anti-anxiety properties of valerian root extract are due to the presence of valerenic acid and valerenol. Incredibly, an herbal supplement such as Valerian could exert the anxiolytic impact as prescribed medicines with the least adverse effects. It has calming and anti-anxiety properties[29].

5.8 *Aloysia triphylla*

Aloysia triphylla belonging to the family of the Verbenaceae would be a persistent, occupied herb native to America that is now grown throughout the Middle East. Traditional medicine has long used *Aloysia triphylla.* This herb is showing a mild sedative effect and aids in the management of anxiety[30]. The flower has a stimulant effect on the brain and is known to relieve abdominal pain[31]. The herb has been discovered to have antioxidant properties[32]. Phytochemical studies of *Aloysia triphylla* aerial parts produced the discovery of various substances, artemether, and hesperidin[33]. Artemis is said to have anti-inflammatory properties. Furthermore, artemisinin has been shown to relax smooth muscles[34]. Hesperidin is a bioflavonoid glycoside that shows a variety of medicinal properties. And showing to resemble antipyretic and analgesic properties[35]. different pathways, such as inhibition of secretion and reduction of eicosanoid synthesis have been proposed to explain such activity. Hesperidin is also discovered to have central nervous depressant effects[36].

5.9 *Citrus aurantium*

Citrus aurantium L is a fruit which is belonging to the family of Rutaceae, also termed as bitter orange (local names: laranjaazeda, laranjacavalo), is utilized in Brazil as remedies and in different states to reduce stress and depression and works as an antiepileptic, with major depression effects on the CNS. extract oils, particularly with citrus substance, are widely employed for treatments of mood and anxiety-like conditions[37], peeling out of extract oil is thought to generate mental calmness[38]. Bitter orange seeds were made up of twenty-two phenolic compounds, such as hydroxybenzoic acids, ferulic acid, flavonoids, quercetin, simple alcohol, and coumarins[39]. Human studies indicate that inhaling various types of oils is beneficial in decreasing psychological stress, anxiety, and cortisol levels in hypertensive patients[40]. The sharp impacts of natural extracts on centrally depressed people and anxiety have attracted the attention of researchers because they may be a viable replacement for synthetic substances that cause sedation, memory changes, and drug interactions[41].

As an important Iranian folk remedy, Echium (*Echium amoenum*) from the Boraginaceae family is commonly employed as a natural remedy, tranquilizer, diaphoretic, and treatment for shortness of breath, sores, and pneumonia[42]. Antimicrobial, antioxidant, analgesic, anxiolytic, antidepressant, and immunomodulatory properties are thought to exist in this plant[43]. *E. amoenum* decoction has also been shown might be effective in the prophylaxis of intense conditions. *E. amoenum* wet light blue leaf has recently been identified as an essential component of alcoholic components such as cyaniding, as well as delphinidin[44]. The most popular anthocyanin, cyanidin 3-glucoside, found in the leaf of *E. amoenum*, reduces PGE1 synthesis and cox-1 expression by suppressing the excitation and hybridization of NF-B condition to the mitochondria[45]. Min *et al.* also evaluated the neuroprotection action effect of cyanidin 2-glucoside. They hypothesized that the positive impact is due to a reduction in brain superoxide reaching the level by inhibiting apoptosis-inducing component discharge in the nucleus[46].

5.10 *Lavandula angustifolia*

Lavender is an established plant with a broad past in the traditional medicine system that is now used pharmacologically nowadays. The component extracted through the condensation process through the new flower extract of the Lavandula plant is commonly fit as a relaxant in therapy[47]. In both animal and human studies, inhaling the droplets of oil and its primary components, terpenes has been proven to have calming effects[48]. The different therapeutic actions of the oil have been reported, along with antiepileptic, antianxiety, anti-suppressive, and conflict impacts[49]. Lavender, on the other hand, is used to treating restlessness, trouble sleeping, and worried ailments of the intestinal tract and stomach as just a tea infusion (i.e., soluble extracts). Lavender also includes aqueous phenolic constituents like cinnamic acid, and glycosides, which are related to the oxidant capacity of Lamiaceae[50].

5.11 *Melissa officinalis*

Melissa officinalis is a tropical plant which is belonging to the family of the Lamiaceae, also known as lemon balm, and is a herb native to the South American region and southwest part. In Iran country, lemon balm is known as "Badranjboyeh" and is found mainly in the regions of Iraq, Golestan, Azarbayjan, Lorestan, and Kermanshah[51]. The soaked or new petals and upper region of the herb are utilized as medication, Melissa has traditionally been utilized as a stimulant, demulcent, carminative, and medical application for wound healing, insomnia, memory boosting, depression, and alleviation of headaches. Lemon balm was also used in traditional Iranian medicine to manage restlessness or anxiety mainly in women and decreased enthusiasm-related activity and anxiety[52]. *Melissa officinalis* was prescribed by Ibn Sina a reputed Iranian researcher, for the mentioned purposes. essential oil's major components are 40% citronellal, 34% citral, and 3% geranial. Furthermore, Melissa contains in low concentrations rosmarinic acid, phenol, three terpinene, flavanone, and glycoside acids. The claimed crude extract of lemon balm, which is commonly utilized in essential oils, is helpful for mild stress. Melissa officinalis, often referred to as lemon balm, is mainly taken for the pharmacological approach to make the mixture for its relaxing of nerve and antispasmodic action[53], but several phytopharmaceutical formulations contain this plant or its derivatives. Due to its flavor, this plant is often utilized in the culinary industry to flavor various items. The person facing neurological illness has recently been high number over the world, particularly in wealthy countries[54]. Neurodegenerative disorders (Parkinson's, Alzheimer's) and mental diseases (depression or anxiety) are among the most common[55].

5.12 *Viola odarata*

Viola odorata is a small flowering plant that seems to be a group of Viola inbred to Africa and Austria that is spread to the United States or Australia. Wood violets[56], pleasant violet, English violet, regular violet, or garden violet are all names for it. This flower's pleasant scent has proven famous across the centuries, especially later Australian age, and is mainly used in the manufacturing of several clinical scents[56]. In the past used to treat anxiety, and sleeplessness, and reduce BP. Violet is mostly used as a herbal medicine for a variety of respiratory illnesses. It can be highly effective in treating asthma, coughs, and sore throats. Recent research has revealed the number of glycosides in Popular flowers, which shows efficacy in the case of angina and bodily problems. The Typical Violet flower syrup possesses antiseptic, anti-inflammatory, laxative, and cough suppressant effects. It can aid with a variety of respiratory diseases, as well as headaches, sleeplessness, dizziness, and tiredness[57]. Viola includes an alkaloid, a flavonoid, terpenoids, methylsalycylate, and mucilage, and rich in vitamins and used as a diuretic agent, as well as other positive effects, but no research on cardiovascular disease efficacy has already been identified[58].

5.13 *Cimicifuga racemosa L*

Governing organizations approved the usage of *Racemosa L.* For a variety of indications, including depressed mood swings[59]. Several research on *C. racemosa* (black cohosh) has demonstrated that it is mainly used in the management of anxiety problems[60]. Triterpene is present in the oil of *C. racemosa*, as are aromatic compounds, tannin, resin, and fatty acids. a strong transmitter of SSRI 2-HT1A and the 3-HT7 target was recently discovered in the rhizomes of *C. racemosa*[61]. In the widespread benefits of *C. racemosa*, particularly at the time of the menstrual cycle, human investigations discovered no major anti-anxiety result in contrast to control. Smaller samples, the selection of cohosh formulation, and the drug employed in these investigations may have been limiting factors[62].

5.14 *Piper methysticum*

P. methysticum G. Foster (kava) has been approved by herbal medicine regulatory organizations in the management of human therapy of moderate to severe points of phobia. It is just linked to stress, phobia, sleeplessness, and comorbid disease[63]. Kava is an Ocean herb that has traditionally been used as an anxiolytic. Among some of the beneficial compounds identified in Kava are kavalactones like kavain, dihydrokavains, and yangonin. Recent research into the mode of action of isolated kavain has indicated activity on the 39/nuclear factor-kappa/cyclo-oxygenase 2 signaling pathway. Kava inhibits voltage-gated ion channels by binding to Na channels in their resting condition and prolonging their unstable[64]. Kavain can suppress MAO-B and prevent noradrenaline uptake produced in the frontal lobe and of rats[65]. Furthermore, showed that dihydrokavain and yangonin have COX-1 and COX-2 inhibitory activities. Lehmann and colleagues conducted clinical research in

1996 that established the benefit of Kava isolate vs. placebo in individuals suffering from anxiety[66] and discovered a substantial decrease in the unstable state of the brain in the Kava when relate to the control group. However, some publications in recent years have suggested that kava may cause hepatotoxicity[67].

6. Other Essential Flavonoids Act as anti-Anxietic Agents

6.1 Apigenin

A 4′, 5, 7-trihydroxy flavone called apigenin is found in fruits and vegetables. Numerous medicinal actions, including antineoplastic, analgesics, and antioxidant effects, have been reported. The anxiolytic potential of apigenin published in several pre-clinical studies. Using a forced swim test on rodents, Nakazawa investigated the antianxiety role of apigenin and discovered that it improved resistance-like behavior in animals, which was demonstrated by the dopaminergic pathway[68]. In a different study, apigenin was discovered to have an antidepressant role in mice tested with the help of an unpredictable chronic model of mice. According to the researcher's analysis, action may be caused by two increases in the expression of the PPAR (peroxisome proliferator-activated receptor), which inhibited the NLRP2 and ILL synthesis[69]. Apigenin's antidepressant mechanism has also been confirmed by its role in upregulating hippocampal BDNF levels and inhibiting the mono-amino oxidase enzyme. Due to its potential to reduce inflammation[70].

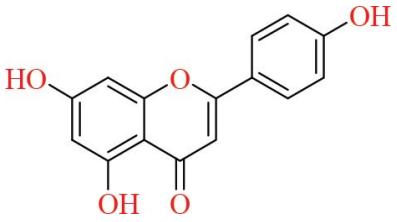

Figure 10. Apigenin.

6.2 Baicalein

Trihydroxyflavone flavonoid baicalein has hydroxyl compounds at positions 5, 6, and 7 of the carbon atoms. The most active flavonoid found is baicalensis, according to research[71]. Baicalein is a potent compound that resembles many actions such as antioxidant and free radical scavenging action, according to numerous reports[71]. According to published research, this flavone significantly shows calming effects and CNS depressant effects and crosses the blood-brain barrier[72]. Additional research has indicated that baicalein, which was purified from the ethanolic extraction of the root of Scutellaria, may suppress the brain, function in a decrease in prostaglandin E2 levels in the brain, as well as act as a potent antioxidant and prevent the development of depressive behavior in mice model. Prostaglandin E2 levels in the brain were found to be reduced in 6 of 48 rodent brains. This substance also serves as a potent antioxidant and aids in the control of chronic stress behavior in mice[73].

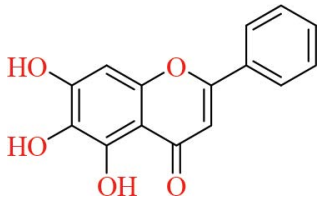

Figure 11. Baicalein.

6.3 Myricetin

Hexahydroxy flavone myricetin has hydroxyl groups substituted at positions 3, 3′, 4′, 5, 5′, and 7 of the carbon atoms. Many substances like, vegetables, dry fruits, rum, and tea are all very plentiful. Its analgesic, antineoplastic, and anti-depressant effects have been verified[74]. In a study, it was discovered that myricetin reduced depressive behavior in mice under stress, which was predicted by the FST. The anti-depressants potential of myricetin was boosted by the findings that this flavonol decreased plasma levels of corticosterone, improved reactive oxygen species enzyme activity in the brain, and enhanced BNF levels[75].

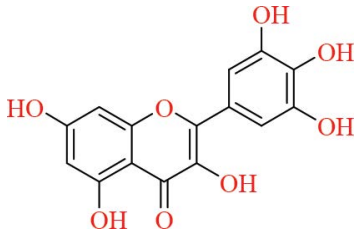

Figure 12. Myricetin.

6.4 Quercetin

Known as a pentahydroxy flavone, quercetin is extremely prevalent in pineapple, garlic, ginger, and red wine[76]. Various flavonoid shows potent free radical properties in the treatment of a variety of illnesses and disorders[76]. Additionally, the anxiolytic role was demonstrated in

a few models of animals, where it was discovered that inhibiting MAO substance increased the concentration of 5HT and nor-epinephrine in synaptic clefts. Quercetin has been shown to have antidepressant properties in diabetic rodents, concluded that it might be used in prophylaxis to treat stress in diabetic conditions[77].

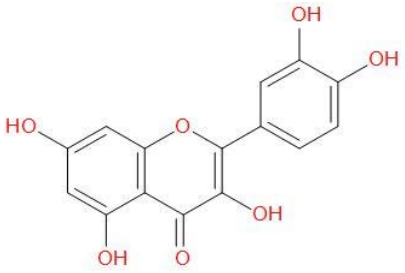

Figure 13. Quercetin

6.5 Rutin

Citrus bioflavonoids such as rutin (tetrahydroxy flavone) are also referred to as sophorin, quercetin, and rutosine. This is comprised of glycoside made up of the flavonoid, myricetin, and the saccharide, with the sugar groups rhamnose and glucose replacing the quercetin's -OH group at position C3. Citrus fruits, vegetables, and plants, including figs, buckwheat, green tea, and others, have all been found to contain[78,79]. It aids in the body's utilization of vitamin C and collagen production. Rutin was published with various activities such as neuroprotection, antioxidant activity, analgesic properties, and anti-tumor properties[78,80]. A compound separates out through the methanolic extraction process of *Schinus moll L.* aerial parts, demonstrating CNS suppressive activity in TST. The anti-depressant effects of rutin were supported by increases in the concentration of 5HT and noradrenaline[80].

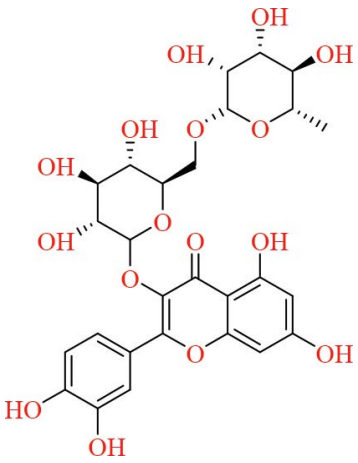

Figure 14. Rutin.

7. Conclusion

Anxiety is still a challenging public health issue. Traditional therapies have their limitations, and the proportion of dependent users is rising. To enhance current treatments for stress, this review emphasizes the need for novel medications. To find a more effective and secure substitute, new plant natural components or phytoconstituents are being researched. To increase effectiveness and lessen negative effects, numerous groups of flavonoids may be taken into consideration as supplements to traditional anxiolytic therapy. Even if the findings about containing natural molecules produced from plants are promising, more study is required to understand the correlations, metabolic, distribution, and psychopharmacological processes of these compounds. However, because the bulk of research uses animal models, clinical evaluation is necessary to confirm the therapeutic effects of novel molecules in anxiety-like diseases in humans.

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