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Title: Recent Advancement in the Management of the Anxiety and Depression: A Review

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ABSTRACT

ORIGINAL RESEARCH ARTICLE

Even though conventional treatments based on monoamines do not always produce complete remission, major depressive disorder (MDD) is still one of the top causes of disability worldwide. An important step forward is the increased utilization of glutamatergic modulators such esketamine (Spravato). For patients with treatment-resistant depression (TRD), Spravato was the first monotherapy to receive FDA approval in January 2025. Novel oral medicines that target mood without common side effects including sexual dysfunction include 5-HT1A receptor agonists like gepirone (Exxua). Zuranolone and other GABA-ergic modulators have also made strides in the treatment of postpartum depression, while psychedelic-assisted therapies like psilocybin and MDMA have shown promising results in clinical trials, providing significant alleviation through neuroplasticity. With the introduction of streamlined 3-minute procedures, transcranial magnetic stimulation (TMS) has became more accessible. One highly accurate method for severe TRD is deep brain stimulation (DBS). Information Technology for Medical Treatment: Recently, the FDA approved digital treatments for prescription use, such as Rejoyn, which provides cognitive behavioral therapy (CBT) by smartphone. Immersive VR-based cognitive behavioral therapy (CBT) is becoming more popular as a means to alleviate symptoms through the provision of secure settings for emotional processing. In order to control neuroinflammation, the latest fads center on the gut-brain axis and anti-inflammatory diets that include probiotics. Another emerging field, precision psychiatry, is utilizing genetic testing and AI algorithms to personalize therapies based on an individual's biological profile. This approach greatly enhances the success rates of those who had previously struggled with standard care. Novel biomarkers can be used to get insight into the underlying faulty circuits. Finally, it also discusses the role of metabolites in anxiety, as it is more focused that the therapies for anxiety disorders may be made possible by the incorporation of biomarkers that may aid in better diagnosis and the development of a classification system for psychiatric diseases that may be linked to the faulty circuits underlying them.

1. INTRODUCTION

Anxiety is a debilitating mental condition that impairs a patient's quality of life and burdens their loved ones and the community. According to the W.H.O. World Health Survey, almost 350 million people worldwide suffer from a mental or behavioural disorder, making it the primary cause of disability worldwide. This disease is identified

as a key contributor to this number. Still, a very small proportion of them obtain basic medical care. By 2030, depression is predicted to rank third in low-income nations and second in middle-income countries for morbidity. One of the most common mental health conditions and a major global source of impairment is anxiety (1). According to the American Psychological Association, tension-filled feelings, anxious thoughts, and bodily changes are the hallmarks of anxiety and stress. Stress is more directly linked to irritability, impatience, and trouble relaxing, while anxiety is more closely linked to skeletal muscle tension, autonomic arousal, and situational circumstances. In talks about global health, traditional herbal medicines have drawn interest as a potential treatment for anxiety. Fifteen plantospecies from 76 taxa and 32 families are the subject of the review. The most often used plant parts for infusions and decoctions are the leaves and flowers. The two families that receive the most mentions are Asteraceae and Lamiaceae (2, 3). To validate the effectiveness of these complementary therapies and learn more about the mode of action of bioactive substances, more study is necessary. The purpose of this review is to emphasise the sedative and sleep-inducing qualities of anxiolytics that come from both domesticated and wild plants (4). Two associated mental health problems that can cause significant impairment are anxiety and sleeplessness (5, 6). Excessive concern, alertness, tense muscles, and a variety of motor and sensory symptoms are all signs of anxiety (7). Furthermore, anxiety may be a factor in the manifestation of bodily symptoms as sweating, headaches, and uncontrollably shaking (8). The symptoms of insomnia include difficulty falling asleep, disrupted sleep, and morning awakenings (9). Since anxiety and other neurological illnesses can be brought on by low levels of GABA in the central nervous system, the neurotransmitter gabama-aminobutyric acid (GABA) is important in the development of anxiety (10, 11). Increasing GABA-A receptor affinity for the benzodiazepine (BZD) site, activating GluAD, and inhibiting GABA-T are some methods for raising GABA levels. However, SSRIs and SNRIs, which are frequently used for GAD, have negative effects that include dependency, nausea, muscular spasms, memory loss, and an increased risk of fractures and accidents (12). Finally, more focused therapies for anxiety disorders may be made possible by the incorporation of biomarkers that may aid in better diagnosis and the development of a classification system for psychiatric diseases that can be linked to the faulty circuits underlying them (13). Given that metabolites are involved in or respond to the majority of bodily activities, studying metabolites (metabolomics) on a wide scale is now thought to be one of the most illuminating ways to explore possible biomarkers (14, 15).

2 CURRENT STATUSES FOR MANAGING THE ANXIETY DISORDERS

2.1 Herbals as Anxiolytics

Many people who suffer from depression or anxiety turn to herbal medicines. Therefore, it's critical to determine whether they produce more benefits than drawbacks. Trial data for Ginkgo biloba, Lavandula angustifolia, Hypericum perforatum, Valeriana officinalis, Crataegus oxyacantha, Eschscholzia californica, Matricaria recutita, Melissa officinalis, Passiflora incarnate, and Piper methysticum were found through a systematic examination of the available literature.

Anthemis arvensis L.

Phytoarvensis lutea L. The European annual herbaceous plant known as chamomile (Anthemisoarvensis L.) is widely used in Italian folk medicine as a sedative, digestive aid, spasmolytic, expectorant, and anti-inflammatory. On the other hand, no scientific studies on the pre-clinical and clinical trials of cornochamomile for the treatment of anxiety and sleeplessness are currently accessible. Consequently, more in-vitro and in-vivo research is needed to determine its mechanism of action and prove its effectiveness as a sedative (16).

Humulus lupulus L.

umuluso lupulus L., often known as common hop, is a perennial herbaceous climbing plant that is indigenous to North America, Europe, and southwest Asia. The leaves of the plant are lobed, and its female flowers are clustered in clusters that resemble cones. The leaves are used to cure dysmenorrhea, stomach problems, and toothaches in traditional medicine. Hop extracts are thought to have neuropharmacological effects because they include molecules that exhibit GABA-like activity and because certain hop

chemicals interact with serotonin and melatonin receptors (17).

Lavandula angustifolia Mill.

Native to the Mediterranean region, lavender (Lavandulaoangustifolia Mill.) is a fragrant annual herb dwarf shrub. The leaves of the plant are densely grey, stellate tomentose, and linear toolanceolate-linear. They are grouped on leafy stalks. In folk medicine, lavender is also used to cure headaches, respiratory, gastrointestinal, and urinary conditions. Recent research has validated the sedative and anxiolytic effects of lavender. After inhalative absorption, mice have been used to study the calming effects of lavender essential oil and its major components, linalool (37.3%) and linalyloacetate (41.6%) (18).

Malva sylvestris L.

Malvaosylvestris L., also known as common marshmallow, is a herbaceous plant that is native to Europe, northern Africa, and southern Asia. It is a globally distributed plant that can grow practically anywhere. Its hard leaves have three to seven deeply lobed leaves, and its vibrant purple-rose flowers can open in clusters of three to five axillary flowers, or they can bloom single. Folk medicine employs common allow for a wide range of purposes because of its medicinal qualities (19).

Clinopodium nepeta L.

It is a perennial herbaceous species that grows upright and is native to southern Europe. Occasionally, the base of the plant may be woody. Lesser calamint is frequently added to soups and salads as a flavouring. The calming qualities of this plant make it useful in traditional phytotherapy for treating toothaches, diarrhoea, and vomiting. It is also used as an emollient (20).

Papaver somniferum L.

It is an annual herb that is commonly grown in many temperate locations of the world today. It is thought to have originated in Asia Minoroor the WesternoMediterranean region. Its leaves are lobed, its aerial parts are glaucous, and its top stem clasps the stem. Its big flowers might be violet, pink, or white, and its fruits are capsules. The plant releases latex throughout its body when it is harmed. Initially known as "opos," derived from the word "juice," the Greeks subsequently gave the latex the name opium. Opium was connected by the ancient Greeks to several deities, including as Death instinct, Soma, and Aurora (21).

Rosmarinus officinalis L.

It is an evergreen plant that originated in the Mediterranean region and has organically expanded over most of Europe. Renal colic, dysmenorrhea, nervous system abnormalities, mood disorders, physical and mental weariness, respiratory problems, and hypercholesterolemia have all been traditionally treated with it in folk medicine. Rosemary has a wide range of biological activities, including antibacterial, anti-inflammatory, antioxidant, and anticancer properties. It has also been demonstrated to help with stress, anxiety, and memory. Rosemary extract is frequently used in aromatherapy to lessen symptoms associated with anxiety and increase alertness (22).

2.2 Conventionally used Anxiolytics

Although numerous kinds of antidepressants, barbiturates, and benzodiazepines have been utilised as anxiolytics, their adverse effect profiles have made them less than ideal anxiety therapies. Anxiolytics that target GABA have been developed by researchers in response to the realisation of the function that GABA plays in anxiety disorders. The recent research being done with drugs that specifically target GABA receptors and their subtypes may provide the long-sought class of safe and effective Anxiolytics (23).

Barbiturates

Paraldehyde, alcohol, and other bromide formulations were among the first anxiolytics. The first barbiturate, barbital, was introduced in 1903, and phenobarbital followed a few years later. Barbiturates are now only seldom used as anxiolytics due to toxicity and dependence problems, but many are still prescribed for the treatment of epilepsy and as sedative-hypnotics. Barbiturates can cause oversedation and cognitive impairment as side effects. Barbiturates can result in death, coma, and anaesthesia at large dosages. Within a few weeks of starting treatment, tolerance to barbiturates may develop, necessitating higher dosages to maintain the intended pharmacologic effect. Actually, patients who have received barbiturates for an extended period of time need to be classified as drug dependent. If barbiturates are stopped suddenly, withdrawal symptoms could include anything

from mild anxiety to severe seizures and even death (24).

Nonbarbiturates

The science of anxiolysis saw little change until 1950, when meprobamate was synthesised. The first nonbarbiturate medication to be widely utilised in the management of anxiety was meprobamate. Similar to barbiturates, this compound and others like glutethimide, methaqualone, and methyprylon were formerly thought to represent significant breakthroughs but later proved to be extremely addictive and lethal in overdose situations (24, 25).

Benzodiazepines

Chronic benzodiazepine therapy may result in psychological and physical dependence. Withdrawal symptoms like anxiety, agitation, restlessness, and tension occur if the medication is stopped suddenly. Benzodiazepines can also cause drowsiness and psychomotor impairment as side effects. A number of medications, especially cytochrome P450 3A4 inhibitors like nefazodone, exhibit notable drug-drug interactions with benzodiazepines by significantly raising their plasma concentrations. Antacids, on the other hand, lessen the effects of benzodiazepines (25).

Tricyclic and Monoamine Oxidase Inhibitor Antidepressants

The discovery that some antidepressants had anxiolytic qualities marked the next advancement in the treatment of anxiety disorders. As early as the 1960s, imipramine, a tricyclic antidepressant (TCA), was shown to reduce panic attacks.It was also discovered that five antidepressants known as monoamine oxidase inhibitors (MAOIs) were useful anxiolytics. Nevertheless, TCAs and MAOIs have a less-than-ideal side effect profile, just like other anxiolytics. Apart from the disadvantage of having a delayed onset of effect (three to five weeks or more), both classes have also been linked to weight gain and orthostatic hypotension. TCAs have a multitude of drug-drug interactions, especially with medications that function as cytochrome P450 2D6 inhibitors, and they can be lethal if overdosed. Compared to other antidepressants, MAOIs may have more severe adverse effects. For example, there is a chance of a drug-food or drug-drug interaction that raises tyramine levels and results in severe headaches and stroke (26, 27).

Azapirones

There are very few agents of the azapirone class, and just one of them—buspirone—has been commercialised. The first readily accessible nonsedative anxiolytic that is not a benzodiazepine is buspirone. Compared to other anxiolytics, buspirone has a far better side effect profile. Buspirone does not cause drowsiness, psychomotor impairment, misuse, dependency, or withdrawal symptoms. It also does not have a fatal overdose potential. Nonetheless, there is still a problem with buspirone's effectiveness. Without a doubt, it is ineffective in treating panic disorder. In an 8-week trial conducted with a double blind and placebo control, Sheehan et al. (2006) examined the effectiveness of buspirone and the benzodiazepine alprazolam in treating panic disorder. 85 of the 101 patients who met the DSM-III-R criteria for panic disorder finished the investigation. When it came to causing a quick and long-lasting improvement in panic episodes, anxiety, phobias, and handicap, alprazolam outperformed buspirone and placebo (28).

3 ACTIVE BIOMOLECULES USED AS ANXIOLYTICS

3.1 Taurine

Taurine, 2-aminoethane sulfonic acid, is classified as aβ-amino acid. It has unique structural features such as thepresence of sulfonic group and its β-form configuration. In the brain, taurine has several advantageous pharmacological effects, including neuroprotective and anxiolytic effects. They investigated the possibility of taurine entering the central nervous system by means of the intranasal route. Tests such as the elevated plus maze, activity cage, and rota rod were used to confirm taurine's impact on anxiety in mice after it was administered intraperitoneally.Using strychnine, picrotoxin, yohimbine, and isoniazid in mice convulsion tests allowed for the possible mechanism of taurine's anti-anxiety action to be characterised. When taurine was given via the nasal route in the elevated plus maze test, there was a noticeable increase in the amount of time spent in the open arms. Furthermore, horizontal and vertical. The intranasal administration of taurine significantly reduced the activity of mice. The convulsions brought on by isoniazid were

unaffected when taurine was given intravenously along with the pretreatment. These findings suggest that taurine has minimal impact on the process of GABA production. Glycine receptorhas a different shape than the GABAA receptor and is another ligand-gated chloride channel. Sedation is produced when the glycine receptor is activated by interacting with glycine, which causes the receptor to undergo a conformational shift and open the chloride channel that is connected to it.These findings lend credence to the theory that taurine can enter the brain through the nasal passage and cause anti-anxiety effects. The suppression of a convulsion generated by strychnine suggests that the anti-anxiety effects of taurine may be mediated by the strychnine-sensitive glycine receptor (29).

3.2 N-Acetylcysteine

A well-known chemotherapeutic medication called cisplatin, also known as cisplatinum or cis-diamminedichloroplatinum (II), is used to treat a variety of tumours, including sarcomas and cancers of the blood vessels, soft tissues, muscles, and bones.Four sets of thirty-two male Wistar albino rats were created: control, cisplatin, NAC, and CIS + NAC. Intraperitoneal delivery was used for all treatments. On the first day, NAC (500 mg/kg) was given to the NAC and CIS + NAC groups, while saline was given to the control and cisplatin groups. The fifth day's treatment plan included giving saline to the control group, treating the CIS group with cisplatin (7.5 mg/kg), treating the NAC group with NAC (500 mg/kg), and treating the CIS + NAC group with both cisplatin and NAC (7.5 and 500 mg/kg, respectively). The tenth day's behavioural testing, which included the elevated plus maze (EPM) and open field (OF) tests, demonstrated that NAC considerably reduced the anxiogenic effect of cisplatin.The hippocampal sections evaluation showed increased oxidative stress (increased lipid peroxidation and decline in antioxidant enzymes activity) and proapoptotic action (predominantly by diminished antiapoptotic gene expression) following a single dose of cisplatin. NAC supplementation along with cisplatin administration reversed the prooxidative and proapoptotic effects of cisplatin. In conclusion, the results obtained in this study confirmed that antioxidant supplementation with NAC may attenuate the cisplatin-induced anxiety. The mechanism of anxiolytic effect achieved by NAC may include the decline in oxidative damage that down regulates increased apoptosis and reverses the anxiogenic action of cisplatin.Based on the results obtained in this study, it is obvious that NAC supplementation along with cisplatin application (in the applied doses) was sufficient to diminish the action of cisplatin on the parameters of cisplatin-induced neurotoxicity estimated in this investigation. NAC administration attenuated the anxiogenic effect of cisplatin, resulting in the reversion of behavioral indicators obtained in both performed tests (Figure 1 and Figure 2) back to control values. This neuroprotective action of NAC was accompanied with the improvement of the hippocampal oxidative status (Figure 3), as well as with the amelioration of cisplatin-induced proapoptotic effects (30).

3.3 Hibalactone

Hibalactone (HB) is a lignan of the class of dibenzylbutyrolactones found mainly in species of Araliaceae, Cupressaceae, andRutaceae families.Hibalactone (HB) is a lignan related to the anxiolytic-like effects of Hydrocotyleumbellata L. However, there is a need to understand better the mechanism of action of this lignan tosupport the ethnopharmacological uses of the species.Oral treatment with HB at a dose of 33 mg/kg showed an anxiolytic-like effect in the LDB and EPM tests. Besides that, the treatment altered the ethological parameters, frequency of head dips, and stretched-attend postures (SAP), important to better describe the anxiolytic profile of HB. Pretreatment with flumazenil (2 mg/kg) reverted the anxiolytic-like effect of HB on LDB and EPM tests. On the other hand, pretreatment with NAN-190 (0.5 mg/kg) not reverted the activity observed. In silico predictions revealed the potential of HB to increase GABAergic neurotransmission. Pharmacophore modelling and docking simulations showed that HB might interact with the a1b2g2 GABAA receptor. Conclusion: Together, the results presented herein suggest that activation of the benzodiazepine site of the GABAA receptor contributes to the anxiolytic-like effect of HB (31).

3.4 Evodiamine

Treatment with the berry-derived Evodia rutaecarpa aqueous extract (ERAE) and its main

molecular constituent, evodiamine, can lessen the negative effects of coffee on excitation and sleep. We merged data from the locomotor activity test, the open field test, and the pentobarbital-induced sleep test in mice that had received a caffeine dosage. We discovered that the amount of caffeine-induced sleep disturbance decreased when ERAE and evodiamine were administered. Furthermore, we discovered that evodiamine considerably reduces hyperlocomotion in the locomotor activity test and inhibits caffeine-induced excitement during the open field test. Further in vitro investigations revealed that the treatment of coffee reduced the production of GABAA receptor subunits in the mouse hypothalamus. The administration of evodiamine, however, dramatically stopped this expression decline. When considered collectively, our findings show that ERAE and its main constituent, evodiamine, offer a great option for the management or avoidance of excitatory states and sleep disturbances brought on by caffeine, and that the GABAA-ergic system plays a role in the mechanism underlying these advantageous effects (32).

3.5 Apocynin

We discovered that giving mice apocynin stopped them from developing an anxiety-like phenotype brought on by FSS. Through investigating the potential pathways underlying this behavioural change, we found that the NADPH oxidase inhibitor apocynin restored the elevated levels of lipid peroxidation brought on by stress in the HPC, PFC, and plasma. Apocynin also inhibited the elevations in hippocampus levels of Hdac1, Hdac4, and Hdac5 that were brought on by FSS. Lastly, the decrease in H3Ac levels brought on by exposure to subchronic stress was inhibited by apocynin. All things considered, these findings imply that NADPH-derived ROS may be involved in the predisposition to experience anxiety-like symptoms following subchronic stress exposure, most likely through epigenetic pathways (33).

4 ANIMAL MODELS USED FOR EVALUATING THE ANXIOLYTICS

Experimental animal models are used in modern biological psychiatry to learn more about the pathophysiology of affective disorders. Current research on anxiolytic drugs primarily focuses on particular molecular factors and pathways within a single phenotypic area. However, using animal models allows for a deeper comprehension of the processes of action. As a result, the operational definition of anxiety in one model may not match the definition of anxiety produced by another in terms of pharmacological response, modifications of the environment, and/or neurological substrates. Similar to people, animals can exhibit many forms of dread and anxiety depending on the circumstances (e.g., acute vs. chronic stress, spontaneous vs. conditioned responses, etc) (34). Rather than studying an entire anxiety subtype, animal models with signs of these diseases can only be used to study and stimulate specific components of human psychopathology.

4.1 Elevated plus maze

The elevated plus maze (EPM), which was first created for rats and more recently expanded to include additional species such guinea pigs, voles, hamsters, and gerbils, is one of the most widely used behavioural tests for studies on anxiety and often used mouse models of anxiety. A number of EPM derivatives have also been developed, such as the unstable elevated exposed plus maze, zero maze, and elevated T-maze. The latter is a recently developed model of extreme anxiety in rats in which all four arms are exposed and oscillate on a horizontal plane (34). With the EPM, anxiety-reducing medications or mouse genotypes (such as CCK2 KO, 5-HT1A KO) can be quickly screened without the need for complicated plans or training. The test has several advantages over alternative paradigms that entail administering shocks or depriving subjects of food or water in order to measure anxiety. Specifically, there is little chance that medication effects on pain threshold or appetite will affect the outcomes of experiments (35).

4.2 The light/dark box

Another popular model of anxiety in mice is the light/dark (L/D) exploration test. This test is based on rats' natural aversion to brightly lit regions as well as their impulsive exploratory behaviour in the face of moderate stressors like light and new environments. Mice are allowed to freely explore two interconnected compartments with different dimensions (2:1), colours (white:black), and lighting (bright:dim) in this

model. As a result, control mice positioned in the region with high lighting will quickly migrate into the dimly illuminated area. Following anxiolytic (BDZ) medication therapy, there is no longer any evident fear of staying in or going to the bright area (36). The light/dark box test is still useful for discovering new targets in the field of anxiety–related disorders.

4.3 Four-plate-test

The four-plate test is predicated on the inhibition of a basic natural continuing behaviour in the mouse, namely, its exploration of unfamiliar environments. The device comprises of four identical rectangular metal plates that make up the floor. If a quadrant crossing occurs, a moderate electric foot shock is delivered to suppress this exploratory behaviour. The experimenter electrifies the entire floor each time the mouse moves from one plate to another, clearly causing the animal to flee. BDZs raise the quantity of penalised crossings that the animal accepts. It is vital to confirm that a medication used in this test has no analgesic effects before drawing any conclusions about it. This is confirmed using a hot-plate device with morphine serving as the control substance (37). This test is particularly helpful in explaining the processes of anxiolytic medications that use agonists or antagonists at the 5-HT, glutamate, choecystokinin, γ-aminobutyric acid (GABA), and corticotrophin-releasing factor receptor levels. The FPT is being utilised more and more to identify potentially novel anxiolytics' anti-anxiety properties.

Table 1: Herbal remedies for the treatment of anxiety and depression

S.No.	Name	Common name	Part used	Dose (mg/kg)	Ref.
1.	*Coriandrum sativum*	Dhaniya	Fruit	50, 100 and 200 mg/kg	38
2.	*Turnera aphrodisiaca*	Damiana	Aerial part	25, 50 and 75 mg/kg	39
3.	*Angelica archangelica*	Canda	Whole plant	200 and 400 mg/kg	40
4.	*Passiflora incarnata*	Wild apricot	Aerial parts	5, 10, 25 and 50 mg/kg	41
5.	*Gloriosa superba*	Flame lily	Whole plant	300 mg/kg	42
6.	*Stachys tibetica*	Himalayan tea	Whole plant	200 and 400 mg/kg	43
7.	*Gelsemium sempervirens*	Carolina jasmine	Dried roots and rhizomes	50, 100, 150 and 200 mg/kg	44
8.	*Actaea spicata*	Baneberry	Dried roots	25, 50 and 100 mg/kg	45
9.	*Plectranthus amboinicus*	Mexican mint	Leaves	250 and 350 mg/kg	46
10.	*Melissa parviflora*	Billilotan	Leaves	100, 200 and 300 mg/kg	47
11.	*Justicia gendarussa*	Willow-leaved justicia	Aerial parts	250 and 500 mg/kg	48
12.	*Citrus paradisi*	Star ruby	Leaves	100, 200 and 400 mg/kg	49
13.	*Amorphophallus paeoniifolius*	Elephant foot yam	Tuber	100, 150 and 200 mg/kg	50
14.	*Fumaria indica*	Indian fumitory	Whole plant	100, 200 and 400 mg/kg	51
15.	*Murraya paniculata*	Orange jasmine	Leaves	20, 25 and 50 mg/kg	52
16.	*Cymbopogon*	Lemon grass	Leaves	100 and 200 mg/kg	53

	citratus				
17.	*Mimusops elengi*	Asian bulletwood	Bark	50, 100 and 200 mg/kg	54
18.	*Abies pindrow*	Himalayan Silver Fir	Aerial parts	100, 200 and 400 mg/kg	55
19.	*Punica granatum*	Pomegranate	Leaves	100 and 200 mg/kg	56
20.	*Ocimum sanctum*	Tulsi	Leaves	1.75, 4.25, and 8.5 mg/kg	57
21.	*Caesalpinia digyna*	Rottler	Roots	80 mg/kg	58
22.	*Vitex negundo*	Chinese chastetree	Roots	100 and 200 mg/kg	59
23.	*Centratherum anthelminticum*	Kalijiri	Leaves	100 and 200 mg/kg	60
24.	*Apocynum venetum*	Sword-leaf dogbane	Leaves	30 and 125 mg/kg	61
25.	*Eucalyptus tereticornis*	Fores red gum	Leaves	100mg/kg	62
26.	*Celastrus paniculatus*	Black oil plant	Seeds	3.2 mg/kg	63
27.	*Brassica oleracea*	Cabbage	Leaves	100 and 200 mg/kg	64
28.	*Nymphaea alba*	White Water-Lily Plant	Flower	100 and 200 mg/kg	65
29.	*Moringa oliefera*	Mango	Leaves	200 and 400 mg/kg	66
30.	*Cyndon dactylon*	Garden grass	Leaves	200 and 400 mg/kg	67
31.	*Lippia citriodora*	Lemon Beebrush	Leaves	50, 100 and 200 mg/kg	68

5 ROLE OF METABOLOMIC BIOMARKERS IN ANXIETY DISORDERS

Anxiety disorders are among the most prevalent mental health issues, according to studies of the global burden of disease. Complex diseases with an unknown etiology are the root causes of anxiety disorders. Numerous factors, including those pertaining to genetics, psychology, biology, and chemistry, are thought to play a part in their origin. Despite the ever-evolving anxiety disorder diagnostic landscape, current treatments have only modest therapeutic efficacy, and diagnostic criteria are based on subjective symptom lists rather than objective biomarkers. One possible step toward creating a system to categorize anxiety disorders according to their underlying dysfunctional circuits is the incorporation of novel biomarkers into current treatment techniques. Illness diagnosis, patient classification in a heterogeneous patient population, therapy effectiveness tracking, disease course identification, and therapeutic target identification are all areas that could benefit from large-scale metabolomics research (69, 70, 71). Worldwide, millions of people suffer from anxiety, making it one of the most prevalent mental health disorders. It manifests itself physically, with symptoms like a racing heart and profuse perspiration, and mentally, with feelings of dread, anxiety, and discomfort. Although our current understanding of what triggers anxiety is limited, new evidence points to a function for specific metabolites in the body. The body's metabolism produces metabolites, which are tiny chemicals. They are crucial signaling molecules that can greatly affect our health and wellbeing as a whole. Various investigations have discovered a link between certain metabolites and levels of anxiety. Among these compounds is the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Research has demonstrated that elevated GABA levels alleviate anxiety symptoms, whilst

low levels amplify them. The neurotransmitter glutamate has also been linked to certain forms of anxiety (72). Anxiety levels can rise when glutamate levels are high because the brain cells are overexcited. In addition, changes in lipid metabolism may have a role in the onset of anxiety disorders, according to research (73). Cell membranes rely on lipids, which are present in abundance and play an important role in keeping them intact. Anxiety symptoms may be exacerbated by disruptions in normal brain function caused by dysregulation of lipid metabolism (74, 75). To sum up, the evidence linking anxiety disorders to specific metabolites is mounting. These results provide encouraging avenues for creating new therapies for this crippling illness, but further study is required to completely comprehend the intricate connection between these metabolites and anxiety.

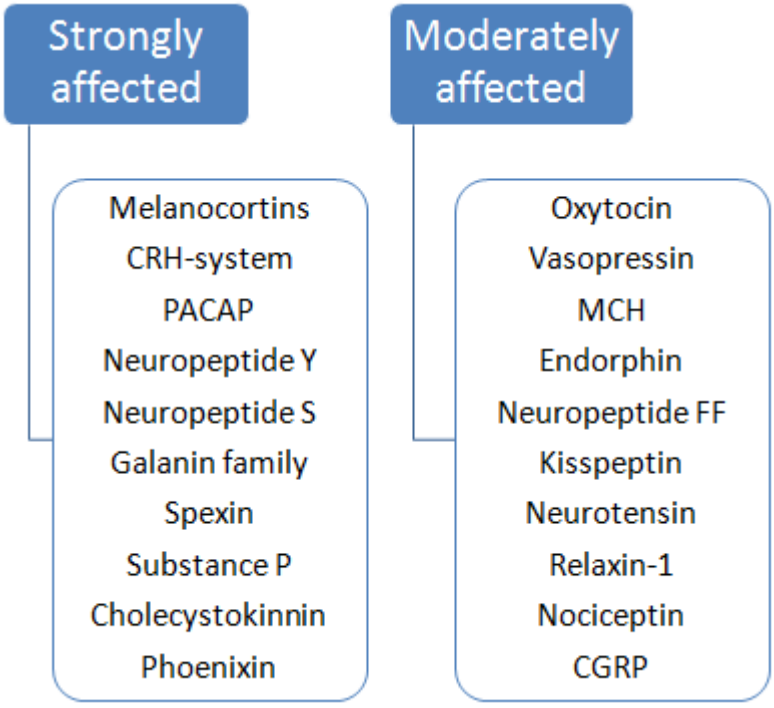

Figure 1: Affected Metabolites Associated to Anxiety

6 CONCLUSIONS

Ultimately, medicinal plants still play a significant role in alleviating anxiety in rural areas, despite the availability of modern medical facilities. Still, we should be worried about the extinction of traditional ethnobotany knowledge and do all we can to preserve it. Cooperation between medical professionals, ethnobotanists, and other relevant authorities is essential for this task. Herbal medicine has been extensively researched and found to have few side effects, making it a practical and affordable option in regions without easy access to medical treatment. Although just a few of natural herbs have demonstrated efficacy as anxiolytics in human trials, they have the ability to alleviate anxiety without significant side effects, in contrast to pharmaceutical drugs. When it comes to anxiety, animal models can provide light on the biochemical pathways at work and pave the road for the discovery of new, potentially life-changing medications. Anxiety has a genetic basis, as shown in human studies, and researchers have used animal studies to try to understand what causes it. There are primarily two types of animal models used in the field of anxiety research. The aforementioned studies on metabolomics' potential application to anxiety disorders show promise for improving diagnosis, illuminating disease origins, and developing efficient treatment strategies. While there are a number of existing barriers to the therapeutic use of metabolites connected to

neurotransmission, oxidative stress, lipid and energy metabolism, glutamine metabolism, and neurotransmission as biomarkers for anxiety disorders, it is worth noting that these compounds may have potential. The main problem is that there are currently no benchmarks for typical metabolite ranges. Gender, diet, lifestyle, medical comorbidities, and drug or medication use are only a few of the factors that impact the metabolic profile; understanding these factors requires additional research. Future study should also investigate metabolomics changes in anxiety as a consequence of psychotherapy treatment to better understand the molecular bases of the effect of psychotherapy on symptom improvement and whether these changes are linked to alterations in metabolomics. Hence, additional research is needed to ascertain if metabolomics might provide biomarkers to improve treatment selection and personalize care for individuals with anxiety disorders.

7 CONFLICT OF INTEREST

None

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