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PHYTOFLAVONOIDS: CONTRIBUTION IN ANXIETY MANAGEMENT

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ABSTRACT

Anxiety disorders are a major worldwide health problem with sizeable psychological, social, and economic costs. It stimulates an anticipatory and adaptive response to challenging or stressful events. In excess, anxiety destabilizes the individual and dysfunctional state results. It is considered to be pathological state when it occurs in the absence of stressful events. It includes general anxiety disorder, social phobia, obsessive compulsive disorder, panic disorder, and posttraumatic stress disorder. Distinct symptoms are displayed for those suffering from anxiety, including shortness of breath, dizziness, heart palpitations, gastrointestinal issues, and an abnormally high body temperature. It typically follow a chronic or recurring course in which full symptomatic remission is uncommon, they are associated with the temporal accumulation of co-morbid disorders and with an increased suicide risk. Anxiety medications can cause unwanted side effects, so some people consider herbal remedies as alternative. Herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Many traditional medicines are derived from medicinal plants, minerals and organic matter. It contains alkaloids, saponins, glycosides and flavonoids etc. The purpose of this review is to provide extensive knowledge about the various phytoconstituents which plays vital role in CNS activity, and possess the anti anxiety potential.

KEYWORDS: Anxiety, herbal medicine, quercetin, rutin, kempferol, alpha pinene, phytoconstituents, phytoflavonoids.

INTRODUCTION

Anxiety disorders are a major worldwide health problem with sizeable psychological, social, and economic costs. Anxiety disorders can promote a crippling focus upon negative life events and make concentration difficult, which can lead to problems in both social and work environments.[1] Anxiety disorders include general anxiety disorder, social phobia, obsessive compulsive disorder, panic disorder, and posttraumatic stress disorder. Distinct symptoms are displayed for those suffering from anxiety, including shortness of breath, dizziness, heart palpitations, gastrointestinal issues, and an abnormally high body temperature.[2] In moderation, anxiety stimulates an anticipatory and adaptive response to challenging or stressful events. In excess, anxiety destabilizes the individual and dysfunctional state results. Anxiety is considered excessive or pathological when it arises in the absence of challenge or stress, when it is out of proportion to the challenge or stress in duration or severity, when it results in significant distress, and when it results in psychological, social, occupational, biological, and other impairment.[3] The disorders typically persist for many years, and are associated with significant personal distress, reduced quality of life, increased morbidity and mortality, and a substantial economic burden. Current treatments for anxiety disorders have modest efficacy many patients do not respond or are unable to tolerate pharmacological approaches and psychological interventions such as cognitive behavior therapy are often limited in availability. While there have been important advances in our understanding of the basic neuroscience of anxiety and its cognitive and behavioral characteristics, at present it is not possible to reliably predict which patient might respond to which treatments and many patients therefore undergo treatment which is sub-optimal. Anxiety disorders typically follow a chronic or recurring course in which full symptomatic remission is uncommon, they are associated with the temporal accumulation of co-morbid disorders and with an increased suicide risk.[4] Anxiety medications can cause unwanted side effects, so some people consider herbal remedies as alternative. Herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Many traditional medicines are derived from medicinal plants, minerals and organic matter.[5] It contains alkaloids, saponins, glycosides and flavonoids etc. These flavonoids plays vital role in CNS activity or on traditional use validation so the present study was conducted to determine the anxiolytic effect.[6]

Phytoconstituents that contributed in anxiety management

(1) RUTIN

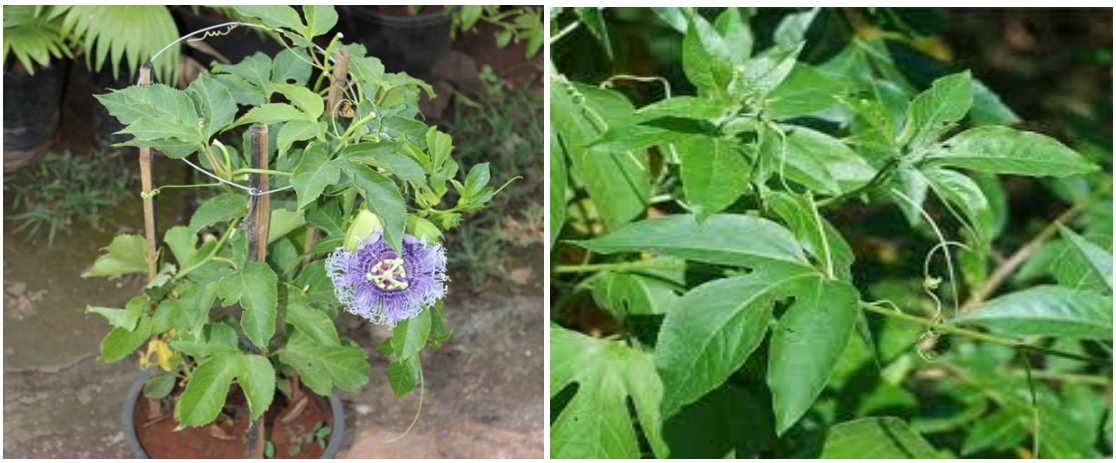
Rutin is a bioflavonoid found in medicinal plants used to reduce anxiety. Evidence is lacking of rutin's anxiolytic like activity, putative mechanism of action, and neural sites of effects. The basolateral amygdala (BLA) is the main brain region that regulates anxiety, through GABAA/benzodiazepine (BDZ) receptors, which are modulated by flavonoids. Therefore, the main aim of this study was to investigate whether the anxiolytic like effect of rutin involves GABAA/BDZ receptors in the BLA. Rutin was administered systemically or microinjected into the BLA, and its effects were assessed. Diazepam was used as a positive control. The mechanism of action was studied using flumazenil or picrotoxin.[7]

It, also called as rutoside, quercetin-3-rutinoside, and sophorin is a citrus flavonoid glycoside found in buckwheat.[8] The name ‘rutin’ comes from the plant *Ruta graveolens*, which also contains rutin. Chemically it is a glycoside comprising of flavonolic aglycone quercetin along with disaccharide rutinose. It has demonstrated a number of pharmacological activities, including antioxidant, cytoprotective, vasoprotective, anticarcinogenic, neuroprotective and cardioprotective activities.[9]

Medicinal plants containing rutin as a phytoconstituent:-

(a) Passion flower

Passion flower is also known as maypop, apricot vine, passion vine, and granadilla. It grows as much as 30 ft (10 m) tall, with a thick, woody stem. The *passion flowers* or passion vines (Passiflora) have a genus of about 400 species of flowering plants and the largest in the family of Passifloraceae. They are mostly vines, with some being shrubs, and a few species being herbaceous. The species of this genus are distributed in the warm temperate and tropical regions of the world, but they are much rarer in Asia, Australia, and tropical Africa. Species of Passiflora have been naturalized beyond their native ranges. *Passion flower* extracts have been classified into several categories of chemical activities like anxiolytic, spasmolytic, hypnotic, sedative, narcotic and anodyne. These extracts are part of a treatment that has successfully treated outpatients with adjustment disorder and anxious mood.[10] Rutin, abundantly found in plants, such as passion flower, buckwheat, tea, and apple.[11]



(A) **(B)**

Figure: (A) Entire plant of *Passion flower* (B) Leaves of *passion flower*

Taxonomical classification of *Passion flower*

Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophytata
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Dilleniidae
Order	Violales
Family	Passifloraceae
Genus	*Passiflora* L.
Species	*P. incarnata* L.

(b) Tea

Tea (Camellia sinensis (L.) O. Kuntze, locally called "Chai" belongs to family Theaceae that is the most consumed beverage in world. The genus Camellia has 82 species and accounts for more than 325 subspecies and 600 varieties that indicate genetic instability and high outbreeding nature of the genus. *Tea* contains many chemicals such as carotene, rivoflavin, nicotinic acid, pentothenic acid and ascorbic acid. Caffeine and tannin are more active among the constituents. Tea used as folk reputation as analgesic, antidotal, astringent, cardiotonic, carminative, CNS stimulants and stomachic used for burns, fever, headache, malaria, smallpox and epilepsy.[12]

(A) **(B)**

Figure: (A) Entire plant of Tea **(B) Leaves of Tea**

Taxonomical classification of *Tea*

Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliphyta
Class	Magnolipsida
Subclass	Dilleniidae
Order	Theales
Family	Theaceae
Genus	*Camellia* L.
Species	*Camellia sinensis* (L.) O.

(2) QUERCETIN

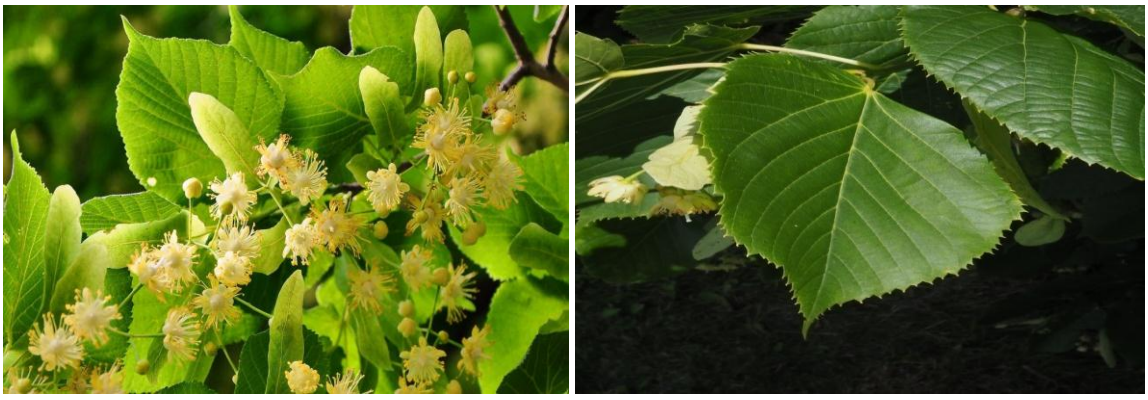
There has been considerable interest in flavonoids as anxiolytic or antioxidant agents with pharmacological effects.[13] Quercetin (3,3′,4′,5,6-pentahydroxyflavone, QUER) is a polyphenolic system commonly found in apples, strawberries, soybeans, broccoli, grapes, citrus fruits, and tea. QUER has been reported to have many beneficial effects on the diseases, such as antiallergic, antirheumatic, anti-inflammatory, and antiviral effects.[14] QUER inhibits ROS producing enzymes and is known to prevent neuronal damage induced by oxidative stress. Also, it has been found to exert anxiolytic properties and can improve cognitive functions in neurobehavioral disorders. Some studies have shown that QUER can improve the neurobehavioral and immunological deficits Also, it has been noted that QUER can easily pass through the blood brain barrier. The researchers have led to the hypothesis that QUER may also be effective for mitigating LPS induced neuropsychiatric symptoms, including anxiety. LPS stimulated inflammatory cytokine cascades have often been used to

study the neurobiological mechanisms of anxiety like behaviors caused by inflammatory mediators and to develop targeted therapies for neuroinflammation.[15]

Plants containing quercetin as a major constituents

(a) Mexican tilia

The *tilia* genus belongs to the tiliaceae family, which consists of 25-80 species and it is mainly distributed in europe and asia, which a new species in north America. In mexico, T. Americana is known as *tilia* and it is distributed in 40 states across both the northern and southern parts of the country. This plant has a wide geographical distribution; however, the populations of the species are confined to the lower mountainous forest that covers less than 1% of Mexican territory. Glycosides of quercetin and kaempferol were characterized as the main active compounds of the inflorescences. Although, it has been demonstrated that these metabolites might facilitate the inhibitory response of the CNS, due to modulating the GABAergic and serotonergic system.[16]



(A) **(B)**

Figure: (A) Entire plant of Mexican tilia (B) Leaves of Mexican tilia

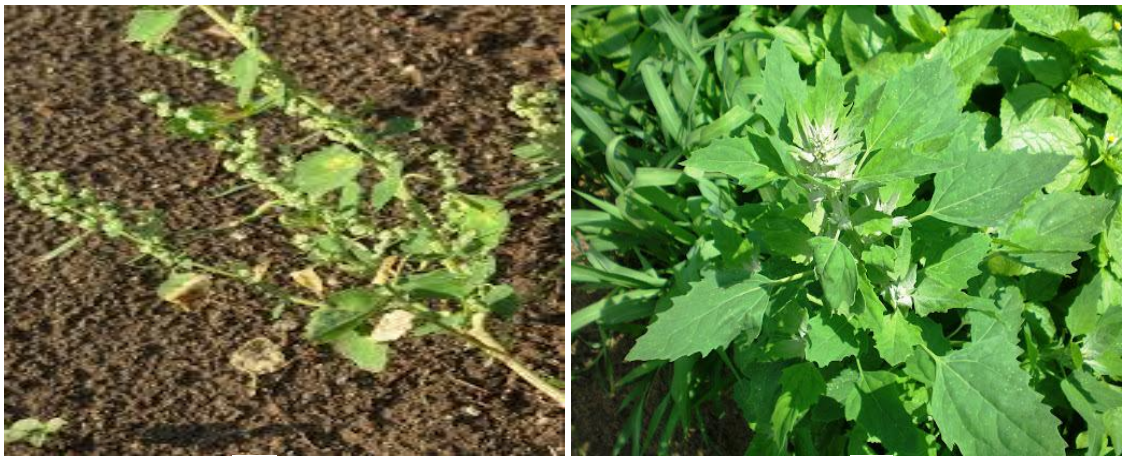
Taxonomical classification of *Mexican tilia*

Kingdom	Plantae
Order	Malvales
Family	Tiliaceae
Genus	*Tilia*
Species	*T. Maxicana*

(b) Chenopodium album

Chenopodium album Linn. Belonging to family *Chenopodiaceae* a native plant of Western Asia, also falls in under the explored category. This plant falls under genus Chenopodium which has a worldwide distribution and contains about 250 species. In India, it is represented

by about 21 species, of which some are cultivated for an end use as vegetable and a few for the grains obtained from the plant. *C. album* have also been reported to grow naturally as weed in the fields of wheat, barley, mustard, gram and other crops. The weed is low growing while the cultivated plants are tall and leafy. The whole young plant has reported uses as food and herbal medicine. *C. album* is known by various vernacular names, viz. *Bathua sag* (Hindi), *Chandan betu* (Bengali), *Parupukkirai* (Tamil), *Pappukura* (Telgu) and *Katu ayamoddakam* (Malyalam). *C. album* is regarded as a prospective wild vegetable and is worth exploration and utilization.[17]



(A) **(B)**

Figure: (A) Entire plant of Chenopodium (B) Leaves of Chenopodium album album

Taxonomical classification of *Chenopodium album*

Kingdom	Plantae
Order	Caryophyllales
Family	Chenopodiaceae
Genus	*Chenopodium*
Species	*C. album*

(3) KAEMPFEROL

Kaempferol, a natural flavone, is found in many plants and has been researched for its wide range of therapeutic actions. It is reported to be particularly effective against ailments involving inflammation.[18] Cancer, and oxidative stress.[19] Through modulation of molecular pathways such as NF-kB, PI3k/AKT, MAPK, Bcl2, Caspase 3, and VEGF.[20] It is of note that kaempferol is capable of exerting beneficial effects against central nervous system disorders as well, such as depression[21] anxiety.[22] And cognitive deficit.[23] Keeping in view the aforementioned reports, the present study was designed to observe the effect of

kaempferol on fear memory processing and associated anxiety in the context of eCB modulation.[24]

The following are the plants constituted Kaempferol

(a) Sansevieria trifasciata

Sansevieria trifasciata is one of the 70 species of sansevieria genus. It is the species of flowering plant in the family Asparagace, native to tropical west Africa. The plant is often referred to as viper's bowstring hemp, snake plant, mother-in-law's tounge, or saint george's word (in brazil). It has significant therapeutic utilization in folk medicine. In Africa, the plant is used as a protetive charm against evil or bewitchment. The use of *Sansevieria trifasciata* in folk medicine for the treatment of different ailments such as ear-ache, ulcer, jaundice, pharyngitis, skin itches, urinary diseases, analgesic and antipyretic.[25] Phytochemical screening of the plant has show the presence of carbohydrates, saponins, glycosides, steroids in the leaves since no data are tilled now reported data in the claimed activities.[26]

(A) **(B)**

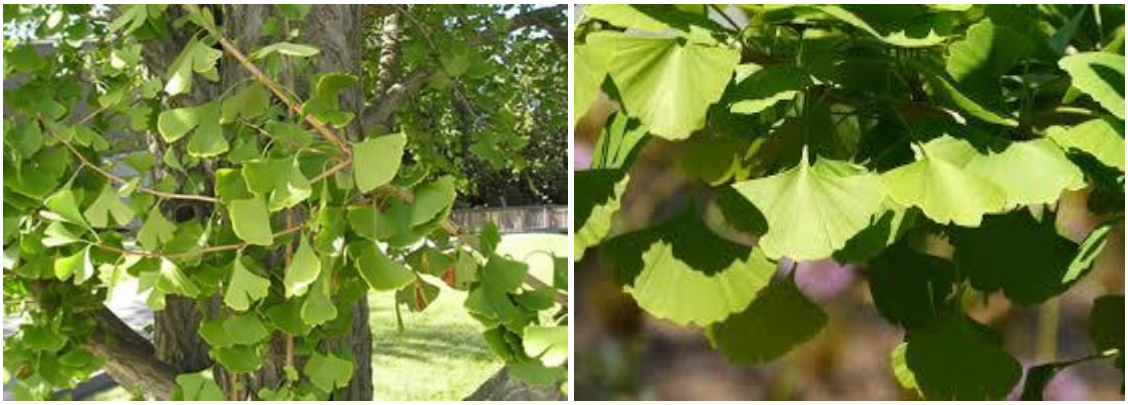
Figure: (A) Entire plant of *Sansevieria trifasciata* (B) Leaves of *Sansevieria trifasiata*

Taxonomical classification of *Sansevieria trifasciata*

Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Liliopsida
Subclass	Liliidae
Order	Liliales
Family	Asparagaceae
Genus	*Sansevieria*
Species	*Trifasciata*

(b) Ginkgo

Ginkgo linn. Is a monotypic genus represented by *G. biloba* linn. Belonging to family Ginkgoaceae commonly known as maidenhair tree or ginkgo tree, originated from china. The tree is considered sacred in china and japan and is cultivated in temple gardens. It has been introduced in india and is occasionally cultivated in gardens. In traditional Chinese medicines, raw ginkgo nuts use to treat asthma, bronchitis, kidney, bladder disorders and bacterial pathogens due to their antibiotic effects. It is also used for treating eye problem, altitude sickness, depression, headache, high blood pressure, edema.[27]



(A) **(B)**

Figure: (A) Entire plant of Ginkgo **(B) Leaves of Ginkgo**

Taxonomical classification of *Ginkgo*

Kingdom	Plantae
Division	Ginkgophyta
Class	Ginkgopsida
Order	Ginkgogoales
Family	Ginkgoaceae
Genus	*Ginkgo*
Species	*G. biloba*

(4) ALFA-PINENE

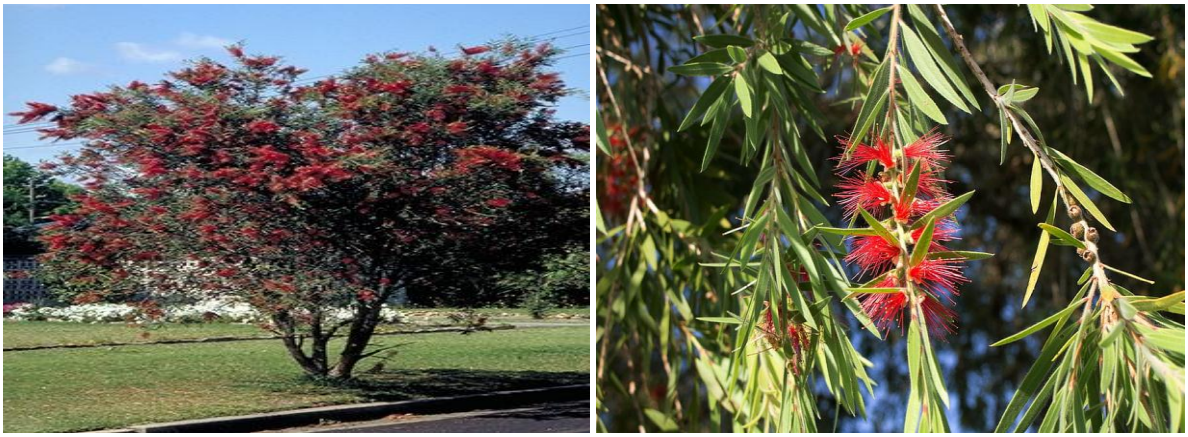
α-Pinene is an organic terpene compound, which is contained in the oil of coniferous trees, and is the major monoterpene in pine trees.[28] *α*-Pinene is widely used as a food-flavouring ingredient[29] and has been approved as a safe food additive by the U.S. Food and drug administration.[30] In addition, *α*-pinene is also contained in essential oils such as in rosemary (*Rosmarinus officinalis*) oil, *Eucalyptus* oil, *Camphor*, *Bupleurum fruiticescens*, *Psidium*, and *Opuntia humifusa*. Indeed, *α*-pinene is considered to have a physiological effect on humans[31], and essential oils containing *α*-pinene have been used to treat several diseases.[32]

However, in humans, odours may lead to behavioural and cognitive changes, so careful interpretation is necessary. Inhalation of essential oils transfer's signals from the olfactory system to the brain, and the brain regulates anxiety, depression, and mood disorders by secreting neurotransmitters such as serotonin and dopamine. Therefore, various plant-derived essential oils have traditionally been used to treat psychiatric disorders such as depression, anxiety neurosis, attention deficit hyperactivity disorder, and bipolar disorder. In addition, it has been reported that *α*-pinene also has anti-inflammatory, antidepressant, anticonvulsant, antioxidant, antitumoral, and antinociceptive effects.[33] Inhalation of *α*-pinene also leads to the accumulation of *α*-pinene in the brain. Although *α*-pinene reportedly acts on rodents' nerves by inhalation, it has not been investigated how *α*-pinene affects psychiatric like behavioural abnormalities. Considering that *α*-pinene acts on the nervous system, *α*-pinene may be a potential therapeutic agent for psychoneurotic diseases including schizophrenia.[34]

Plants containing α-pinene as a major constituents

(a) Callistemone viminalis

Callistemon viminalis (weeping bottlebrush) belongs to family Myrtaceae. It is also known as cheel. C. genus *Callistemon* consists of about 34 species around the world, out of which 10 species are found in India. *Callistemon viminalis* is widely distributed across the world but it is more prevalent in tropical Asia, Australia, Sri Lanka, South America, and India.[35] Viminalis is an important medicinal plant, commonly used for traditional healing. This medicinal plant is also used in medical conditions like stomachaches, skin infections, and respiratory condition.[36] *Callistemon viminalis* is edible, and its leaves act as tea substitute and have adelight fully refreshing flavour and fragrance.[37]



(A) **(B)**

Figure: (A) Entire plant of Callistemone viminalis

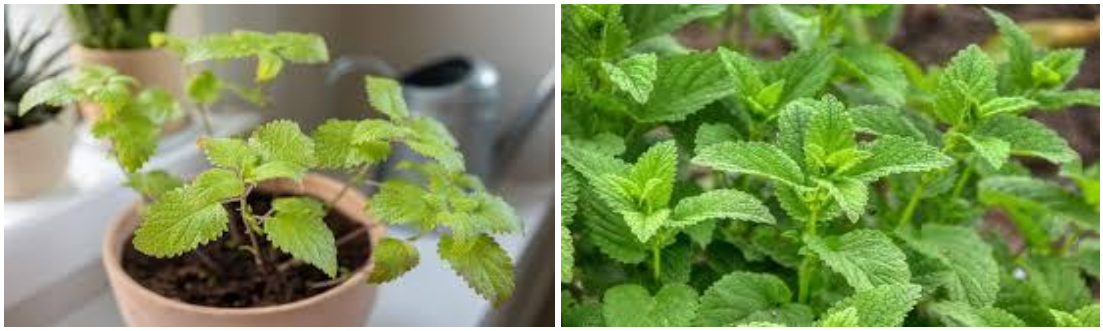
(B) Leaves of Callistemon viminalis

Taxonomical classification of *Callistemon viminalis*

Kingdom	Plantea
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Rosidea
Order	Myrtales
Family	Myrtaceae
Genus	*Callistemon*
Speicies	*Callistemon*

(b) Lemon Balm (Melisia officinalis)

Lemon balm (Melissa officinalis L.) belongs to the mint family and it is indigenous of southern Europe, Mediterranean region, western asia, and north Africa. Lemon balm is non cultivated worldwide. Currently in india *lemon balm* is cultivated in Kashmir, uttrakhand and some part of south india.[38] *M. officinalis,* including its central nervous system effects. Regarding its neurocognitive effects, cholinergic nicotinic and muscarinic receptor binding in human brain homogenates varied considerably across strains of *M. officinalis.*[39] An extract with negligible cholinergic receptor binding produced, in humans, behavioural results consistent with its long traditional use as a mild sedative/anxiolytic.[40] The mood/anxiolytic effects of *lemon balm* may be attributable to known interactions with GABA A receptors.[41]



(A) **(B)**

Figure: (A) Entire plant of Lemon balm **(B) Leaves of Lemon balm**

Taxonomical classification of *Lemon balm*

Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Lamiales
Family	Lamiaceae
Genus	*Melissa*
Species	*M. officinalis*

CONCLUSIONS

Considering that oxidative stress is unequivocally associated with the advancement of anxiety, the reported data suggest that the utilization of these flavonoids may help in reducing the symptoms of anxiety, notably via supplementation of dietary flavonoids in which they are significantly related with the minimization of anxiety risk due to their great antioxidative natures. Regrettably, advanced investigations are needed to fully understand the mode of action to neuroprotection, biotransformation of their metabolites in the body, and interaction properties with receptors related to anxiety.

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