Review Article

Therapeutics Effects of the Genus *Citrus* in Anxiety Disorder

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Abstract

Background: Anxiety and mood disorders are among the mental health diseases that have exponentially increased in prevalence owing to the hectic and stressful lifestyle. In addition to negatively impacting people's physical health, this has resulted in a major psychological, social, and financial burden. A lot of emphasis has been placed on dietary and lifestyle modifications in the ongoing search for medication-free treatments. Investigating the connection between the consumption of specific fruits and vegetables and mental health issues such as depression has produced some intriguing and occasionally encouraging results. The genus *Citrus* with over 1300 species of plants is enriched with a plethora of polyphenolic compounds on the one hand and multicomponent volatile oil content on the other hand.

Purpose: The current work is centered on examining the range of phytoconstituents found in various citrus species—both underutilized and utilized—as promising avenues for future anxiolytic research. The work also details the proposed pharmacological mechanisms of isolated components and clinical trial advancements of selected citrus species.

Methodology: Various databases, including PubMed and ScienceDirect, were used to search and collect relevant literature published in the past 10 years (2014–2024). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria recommended for drafting methodical reviews were followed.

Results: Initially, 1791 articles were collected through an electronic database search, irrelevant titles/abstracts (1449) and other types of articles (05) were excluded. Out of 342 assessed reports, 187 duplicate articles were excluded. Finally, list of 67 articles was included in this narrative review.

Conclusion: Although research and development, as well as the commercial use of several citrus varieties, have attracted some interest recently, analyzing neglected citrus species closely can help to improve their processing into well-known anxiolytic leads by revealing their untapped potential. The work emphasizes the extensive exploration of underutilized citrus species, which have a rich bioactive pro file and enormous potential in pharmaceutical research and development.

Keywords

Anxiety, anxiolytic, *C. maxima, C. medica, C. reticulata*, Citrus

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Introduction

Mental health illnesses are becoming more widely acknowledged as public health concerns on a global scale. Mental health problems include illnesses such as abnormally high levels of anxiety, sadness, stress, insomnia, cognitive impairment, and other conditions. Notably, the working class has seen a rise in the incidence of stress-related symptoms in a wide range of employment. The most common mental health conditions are anxiety and mood disorders, which are linked to a significant psychological, social, and economic burden, as well as an elevated risk of physical illness.[1,2] Increased fruit and vegetable intake significantly impacts how diet and health are related. Research has indicated that those who consume more fruits and vegetables have a lower risk of mental health problems such as anxiety, depression, and poor mood.

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Polyphenol-rich fruit-based therapies may improve brain function.[3–5] Consuming a lot of fruits and vegetables also increases the likelihood of experiencing the best possible mental states, such as happier, more upbeat moods, life satisfaction, and socioemotional flourishing—a phrase used to characterize emotions of fulfilment, meaning, and purpose in life.[6] Several citrus species are significantly effective at reducing depressed symptoms, normalizing neuroendocrine hormone levels, and boosting immunity.[7,8]

Genus Citrus

Etymology and Taxonomical Aspects

Throughout the world, both tropical and temperate regions produce *Citrus*, a genus of evergreen fragrant shrubs and tiny trees of the Rutaceae family. A variety of secondary metabolites, including phenolic acids, flavonoids, carotenoids, coumarins, limonoids, glucarate, and essential oils (EOs), are found in abundance in citrus fruits, blossoms, and leaves.[9] Though citrus is one of the evergreen crops, because of the lack of scientific confirmation and incomplete research into citrus taxonomy, the potential medical benefits of the citrus species in India have not yet materialized.[10] The literature is disorganized, even though citrus and its allies appear to have been the subject of a significant amount of research. This is mostly because there is a dearth of fundamental taxonomic work, which has resulted in inconsistent nomenclature. Scientists have been reluctant to study a group of plants for which nearly all herbarium specimens are of cultivated varieties with insufficient ripe fruit preservation in alcohol because mature oranges and lemons do not make acceptable herbarium specimens. Subsequently, the issue is attributed to the emergence of several hybrids of different citrus species as a result of clonal propagation techniques such as apomixes and grafting.[11,12] Prior genetic research had determined that the three original or basic species—the citron (*Citrus medica* [*C. medica*]), the pomelo (*Citrus maxima* [*C. maxima*]), and the mandarin (*Citrus reticulata* [*C. reticulata*])—were where all other species originated.[13] Numerous species were created by extensive hybridization and long-term breeding; each species is distinguished by its unique metabolism, producing various secondary metabolites.[14] Table 1 provides a glimpse of hybridization of different citrus species.

Ethnomedicinal Evidence of the Genus Citrus

Constipation, cramps, diarrhea, colic, bronchitis, tuberculosis, cold, cough, obesity, menstruation disorders, angina, hypertension, anxiety, depression, and stress are just a few of the conditions for which the *Citrus* has been traditionally used.[21] In Ayurvedic pharmaceutics and therapies, many *Citrus* species are used. *C. medica* Linn. (Bijapur) is an antiemetic, appetizer, and cardio-stimulant. *C. jambhiri* helps with digestion and acts as an antidiarrheal. Regarding Rasa Shastra (Ayurvedic pharmaceutics), citrus varieties are helpful in the processes of cleansing, burning, and shaking necessary to prepare various Ayurvedic formulas.[22] *C. maxima* and *C. grandis* are commonly used in the traditional Chinese medicine system to aid in digestion and get rid of cough, sputum, acute diarrhoea, and chronic dysentery. The citrus species, such as *C. maxima* and *C. limon*, are used as antidotes for venom and poison in the Mediterranean region.[23]

Role of the Citrus Species Specific to Anxiety

Methodology for Literature Search and Collection

Various databases, including PubMed and ScienceDirect, were used to search and collect relevant literature published in the past 10 years (2014–2024). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria recommended for drafting methodical reviews were followed. The major keywords, such as *Citrus* genus, citrus plant, *in vivo* and *in vitro* studies, and preclinical, and clinical trials were used during the search of the literature in various databases. Initially, 1791 articles were collected through an electronic database search, irrelevant titles/abstracts (1449) and other types of articles (05) were excluded. Out of 342 assessed reports, 187 duplicate articles were excluded. Finally, 67 articles were included in this narrative review as represented in the flow chart (Figure 1).

Citrus sinensis

Originating in Asia, *Citrus sinensis* (*C. sinensis*) is one of the most widely grown citrus cultivar groupings worldwide, making up over 70% of all citrus species produced annually. Traditionally, it has been used to cure conditions such as colic, constipation, cramps, diarrhea, bronchitis, tuberculosis, colds, coughs, obesity, menstruation disorders, angina, hypertension, anxiety, depression, and stress. Its EOs are included in the list of aromatherapy agents that can help reduce sadness, tension, and anxiety.[24,25] Volatile oil from the *C. sinensis*, when administered orally, has been shown to have positive benefits on anxiety in a clinical investigation, including individuals with anxiety.[26-28] In Wistar rats, sweet orange (*C. sinensis* oil) scent exhibited anxiolytic-like properties. Following a 5-minute exposure to the orange scent (100, 200, or 400 μL) in a plexiglass chamber, the animals were immediately subjected to behavioral assessments. *C. sinensis* oil exhibited anxiolytic effects at all dosages.[29] Oral *C. sinensis* caused anxiolytic and antidepressant-like reactions in mice, suggesting changes in central serotonergic system activity and olfaction are linked to the anxiolytic effect.[30] Research conducted *in vitro* has demonstrated that EO from its peels has a soothing impact on the neurological system, making it

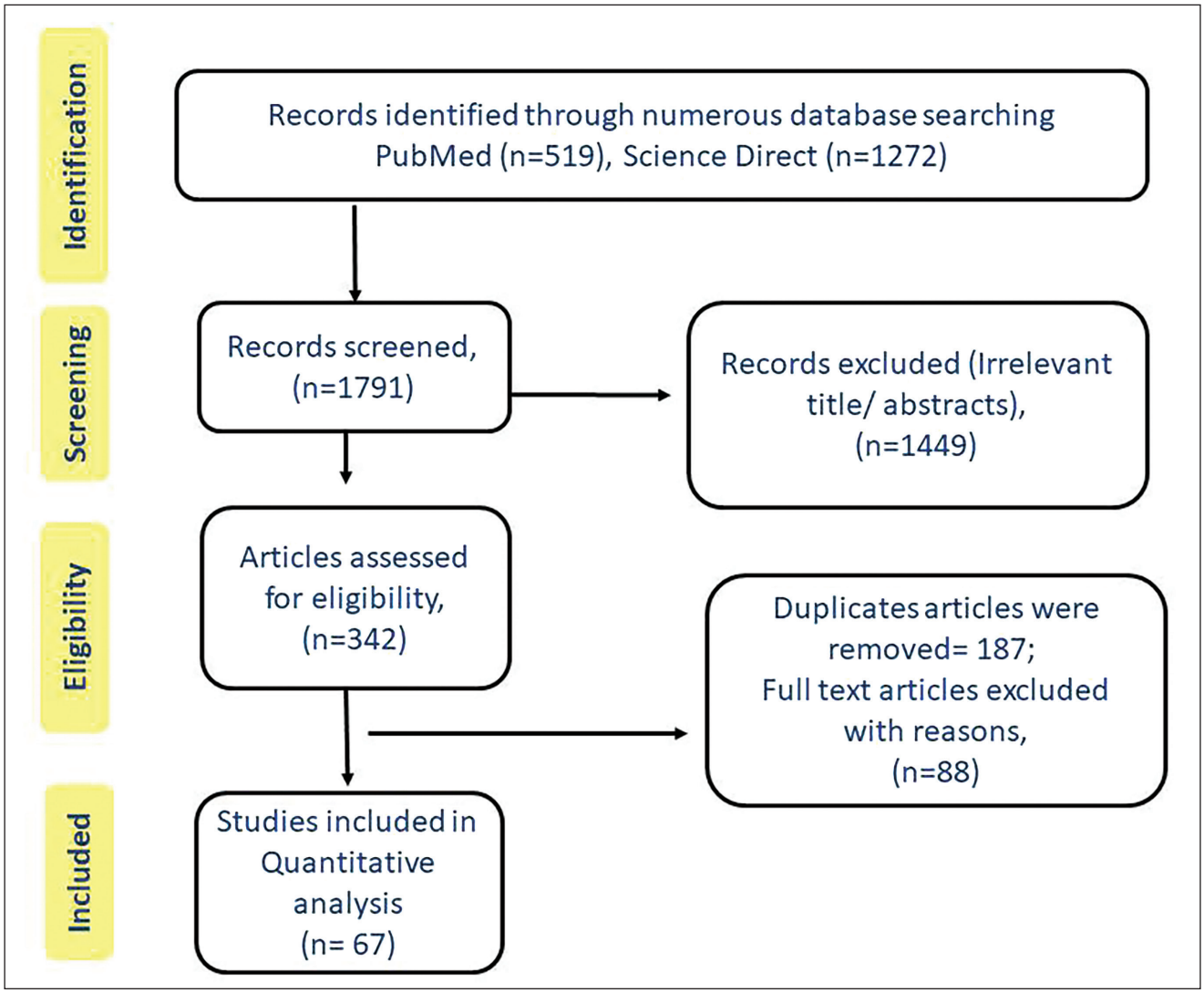


Figure 1. Structural Outline of Search Criteria in Article Selection.

Table 1. Citrus Species and Their Hybridization Status.

Citrus Species	Hybrid Species	Common Name(s)	Reference(s)
Citrus limetta	*Citrus medica* x *Citrus aurantium*	Sweet lime	15
Citrus sinensis	*Citrus reticulate* x *Citrus maxima*	Sweet orange, navel orange	16
Citrus aurantium	*Citrus reticulate* x *Citrus maxima*	Sour orange, bitter orange, Seville orange, bigarade	17
Citrus bergamia	*Citrus aurantium* x *Citrus limon*	Bergamot, sour orange	18
Citrus latifolia	*Citrus aurantifolia* x *Citrus limon*	Persian lime, Tahiti lime, seedless lime	19
Citrus limon	*Citrus aurantium* x *Citrus medica*	Lemon	20

helpful in reducing tension and anxiety.[31] The behavioural assessment of nitrergic system mediation was conducted by co-administering L-arginine (200 mg/kg, i.p.) from Sigma and *C. sinensis* EO. The anxiolytic-like action of *C. sinensis* EO was mostly because of nitrergic neurotransmission.[32] In humans, orange scents in the air decreased anxiety and elevated patients' moods as they awaited dental care.[33]

Citrus aurantium

It is said to have originated in Syria and eastern Africa.[26] Compared to other citrus species, *C. aurantium* has a thicker peel with more EOs and pectin content than sweet orange peel.[34] The most prevalent phenolic chemicals in *C. aurantium* peel were ferulic and p-coumaric acids, whereas

limonene is the main volatile compound discovered in the peel.[14] According to published research, neohesperidin, hesperidin, narirutin, and naringin are the flavonoids that are most prevalent in *C. aurantium* seeds.[35] Limonene, a common terpene present in citrus fruits, is thought to work through dopamine and γ-aminobutyric acid (GABA) to relieve stress and mood disorders.[36,37] It has been observed that oral treatment of *Citrus aurantium* (*C. aurantium*) L. oil extract enhances anxiolytic behaviors in mice via the interaction with the 5-HT1A receptor.[38] In a single-blind, randomized controlled experiment, individuals undergoing coronary angiography found that inhaling *C. aurantium* EO effectively reduced their levels of tension and anxiety.[39] *C. aurantium* EO inhalation has been reported to significantly lower the heart rate, systolic and diastolic blood pressure, and other critical indicators of anxiety.[39–41] A study involving 60 diabetic patients found that bitter orange extract inhalation aromatherapy, compared to the control group, could effectively relieve anxiety and fatigue.[42] A trial using *C. aurantium* EO nebulization among 51 volunteers showed that EO maintained controlled anxiety levels during the simulated public speaking method compared to the control group.[43] According to a study,[44] *C. aurantium* had an anxiolytic effect and helped chronic myelogenous leukemia patients' symptoms of anxiety.

Citrus reticulata

Commonly referred to as mandarins, these are the ancestors of many hybrids citrus cultivars, having either naturally hybridized or through breeding from one of the original citrus species, according to genetic research.[45] They are typically easy to peel and separate into pieces because of their thin, loose peel, and little white mesocarp. Mandarin, in general, can vary from oblate to round to oblate-necked depending on its variety, unlike normally spherical oranges.[46] The fruit helps with vomiting and has laxative, astringent, aphrodisiac, and tonic properties. The fruit peel has long been used as an antiscorbutic, carminative, stomachic, astringent, and tonic.[47] The oral administration of *C. reticulata* EO reduced anxiety in mice and prolonged sleep induced by ether inhalation.[48] Its EOs have been examined for their anxiolytic impact on adult zebrafish (*Danio rerio*). The results showed that its EOs tended to alleviate anxiety using the light–dark test.[49] It has been observed that the mixture of the primary active ingredients, p-cymene, α-terpinene, terpinen-4-ol, and α-terpineol cymene, in its EOs, has anxiolytic effects.[50] *C. reticulata* fruit extract and peel EO exhibited anti-anxiety properties in a chronic mild stress-induced mouse model by modifying the gut microbiome.[51] The dried peel extract of *C. reticulata* showed the anxiolytic-like effect comparable to fluoxetine in an increased open-platform test anxiety paradigm, suggesting that they may function pharmacologically through the serotonergic neurotransmission route similarly to fluoxetine. Additionally, it suggested that hesperetin, the main chemical component, may have a direct and indirect function as an active principle in the antianxiety-like actions of hesperidin.[52] It is said to relieve the chronic stress of restraint and reduce the damage that lipopolysaccharide causes to the hippocampal and frontal cortex of mice.[53]

Citrus bergamia

It is an aromatic citrus fruit that, depending on how ripe it is, can be lime green or yellow in color. Bergamot orange was discovered to be a likely hybrid of bitter orange and lemon through genetic studies into the evolutionary roots of current citrus varieties.[19] According to a number of sources, bergamot was frequently used in traditional medicine as an antipyretic and anti-inflammatory agent and to cure toothaches, burns, varicose veins, furunculosis, and wounds. It has been observed that bergamot EOs have calming/anxiolytic effects in rats during open-field activities.[54] The 5-HT1A serotonergic receptors have been linked to the anxiolytic-relaxant effects of bergamot EO in the open field and elevated plus maze tests.[55] It has been observed that the combination of antioxidant, anti-inflammatory, and GABA-regulatory properties of bergamot EO can reduce the anxiety-like behavior of rats exposed to aluminum trichloride.[56,57] Bergamot oil inhalation significantly reduced anxiety and sleep quality in surgical intensive care unit patients, as evaluated using the "State-Trait Anxiety Inventory" and "Richard–Campbell Sleep Scale."[58] In a related study, postpartum women's depression symptoms and sleep quality were both improved by EO inhalation.[59]

Citrus latifolia

The Persian lime is a triploid hybrid of the lemon (*C. limon*) and Key lime (*C. aurantifolia*). Compared to the Key lime (*C. aurantifolia*), the Persian lime is bigger, has thicker skin, and has milder citrus aromas. When compared to key limes, Persian limes are more advantageous in commercial agriculture because of their greater size, lack of seeds, hardiness, lack of thorns on the branches, and longer fruit shelf life. Compared to key limes, they are less acidic and lack the bitterness that gives key limes their distinct flavour.[60] Because of its antibacterial, carminative, diuretic, and eupeptic properties, the lemon EO has been utilized since ancient times.[61] To assess its anxiolytic efficacy, *C. latifolia* EO was put through standard experimental methods using male Swiss mice, such as marble burying tests and light–dark box testing. Positive results on slight-dark box characteristics indicated that the oil was beneficial for treating generalized anxiety.[62]

Citrus limon

Before vitamin C was discovered, scurvy was customarily treated with *C. limon* fruit juice or lemon juice.[20] Lemon

juice has other use in traditional medicine, such as treating irregular menstruation, high blood pressure, and the common cold. In addition, *C. limon* EO is a well-known cough treatment.[63] Its EO's anxiolytic properties were tested on mice using standard anti-anxiety animal models, and the findings suggested that the anxiolytic properties of the oil could be mediated through benzodiazepine-type receptors.[64] Mice given *C. lemon* EO orally showed increased dopamine concentrations and decreased dopamine turnover in the striatum and hippocampus, affecting emotions' neurotransmission pathways.[65] It has been demonstrated that the volatile components of *C. limon* EO promote the release of monoamines in rat brain slices.[66] High in alkaloids, its leaf extract has been shown to have a potential anxiolytic effect, presumably as a result of its interaction with neurotransmitter systems that regulate anxiety.[67] *C. limon* has been examined for its behavioral effects in rats at three distinct dosages (0.2, 0.4, and 0.6 ml/kg, regarded as low, moderate, and high doses). The results indicated that *C. limon* at a moderate dose had the anxiolytic effect.[68] GABA-A receptor modifying qualities of *C. limon* oil have been linked to its anxiolytic and sedative effects.[69]

Citrus Maxima

Folk medicine uses *C. maxima* leaf oil to cure skin conditions, headaches, and stomach aches.[70] Fruit peels are frequently used in traditional medicine to treat epilepsy, cough, edema, and other conditions. They are also used for cosmetic purposes.[71,72] *C. maxima* fruits are used to treat mental abnormalities, asthma, leprosy, hiccups, coughs, and epilepsy; blooms are used to treat anxiety and sleep difficulties. Its methanolic extract at 400 mg/kg has been reported to exhibit anti-anxiety effects using the hole board and elevated plus maze methods in animal models.[73]

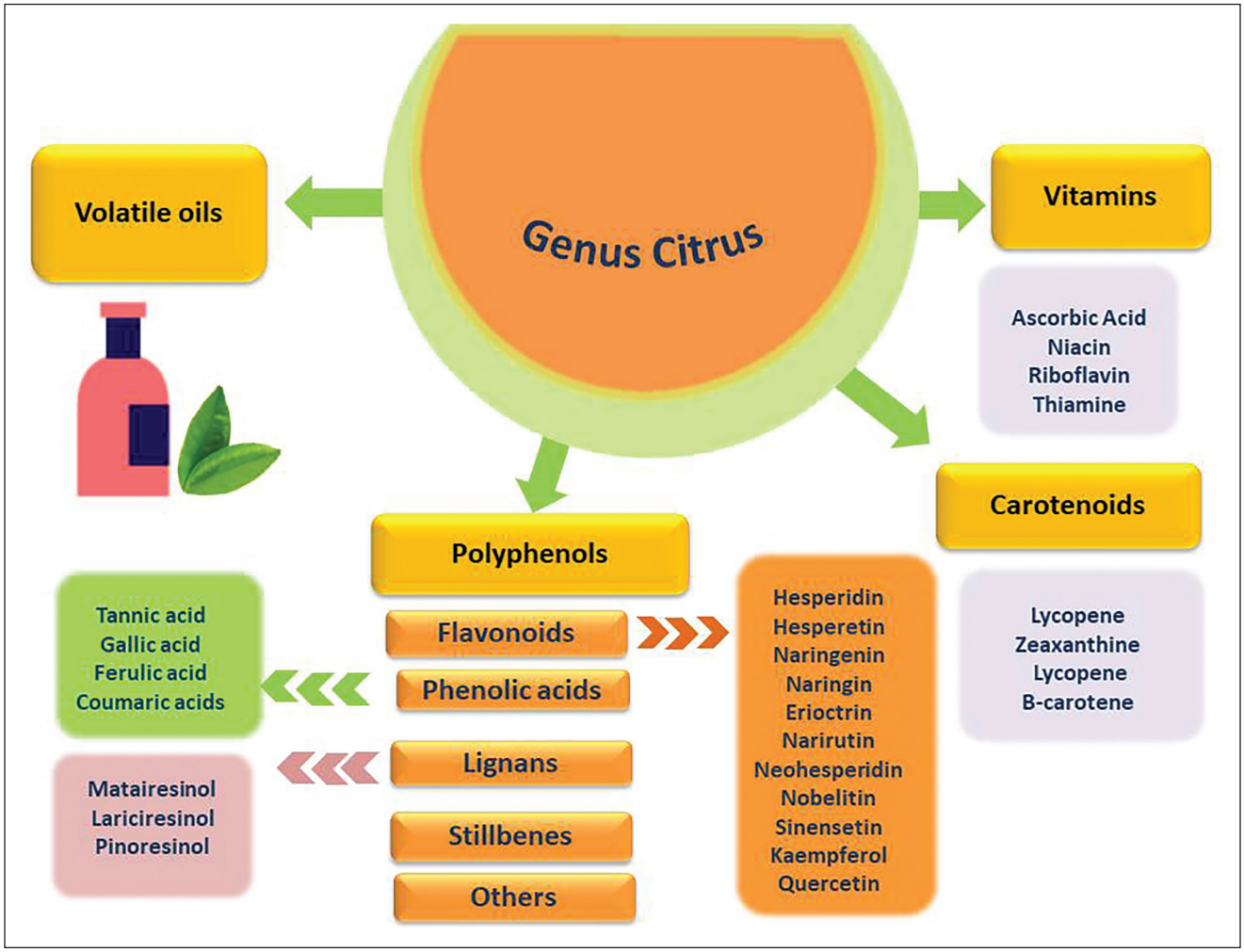
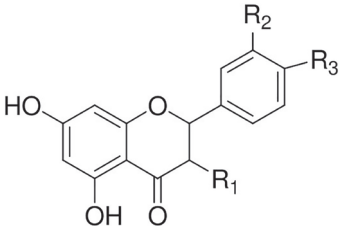
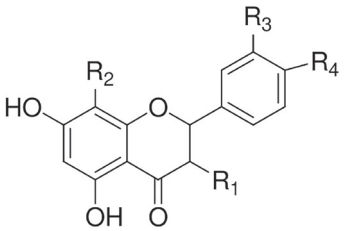


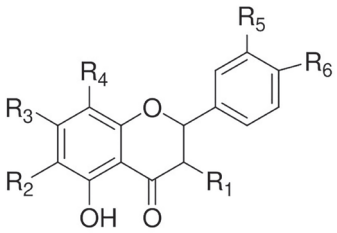
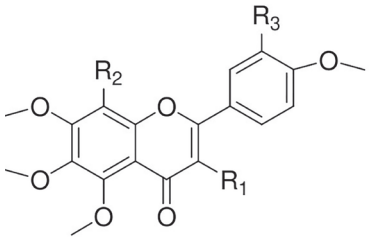
Figure 2. Overview of Phytochemicals Reported in Genus *Citrus*.

Table 2. Anxiolytic Actions of Isolated Citrus Aglycones in Anxiety Disorder.

Phytoconstituent	Chemical Structure	Anxiolytic Action	Reference(s)
Flavanone			
Hesperetin	R1=H R2=OH R3=OCH_3	Via modulation of dopaminergic innervation in the striatum; via activation of the Nrf2/ARE pathway, reduced high glucose-induced neuronal impairments in diabetic rats, exhibiting anxiolytic effects.	77–79
Naringenin	R1=H R2=H R3=OH	Enhances antioxidant response and increases protein level of nuclear factor E2-related factor 2 (Nrf2), protecting against neurodegeneration and reducing oxidative stress and inflammatory effects.	80–84
Taxifolin	R1=H R2=H R3=OH	Inhibition of monoamine oxidase (MAO).	85
`Flavone			
Acacetin	R1=H R2=H R3=H R4=OCH_3	GABAnergic & neuroprotective mechanisms involved in effectiveness against anxiety; Reversible monoamine oxidase activity leading to effectiveness in anxiety and depression.	86, 87
Isoscutellarein	R1=H R2=OH R3=H R4=OH	Reported for exhibiting human monoamine oxidase isoforms in docking studies.	88
Luteolin	R1=H R2=H R3=OH R4=OH	Anxiolytic effects by increasing norepinephrine and decreasing serotonin levels in the structures within the fear circuit, medial prefrontal cortex, and hippocampus. Through the reduction of brain-derived neurotrophic factor (BDNF), superoxide dismutase (SOD), catalase (CAT), and neurotrophic factor in the hippocampus and prefrontal cortex, suggesting effectiveness in anxiety due neuroprotective, anti-inflammatory, and antioxidant qualities. Suggested neuroprotective properties via generating pro-inflammatory cytokines.	89–91
Kaempferol	R1=OH R2=H R3=H R4=OH	Anxiolytic actions, possibly through GABAnergic mechanisms.	92, 93

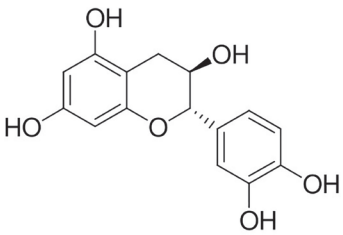
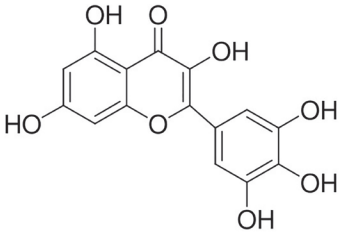
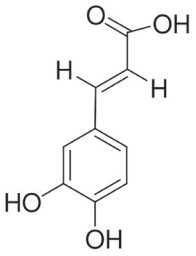
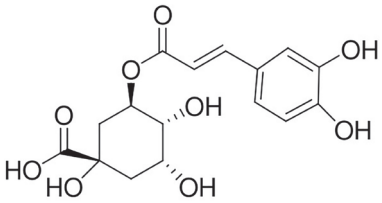
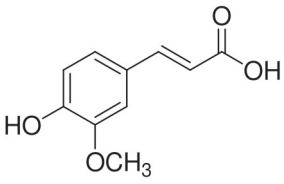
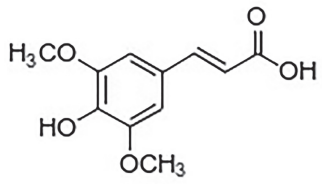
(Table 2 continued)

(Table 2 continued)

Phytoconstituent	Chemical Structure	Anxiolytic Action	Reference(s)
Quercetin	R1=OH R2=H R3=OH R4=OH	Acts by attenuation of hypothalamus-pituitary-adrenal (HPA) axis deregulation. Reduction of anxiety through the mitigation of neuroinflammation and mitochondrial dysfunction and regulation of brain-derived neurotrophic factor (BDNF) and decreased the inducible nitric oxide synthase (iNOS).	94–96
Apigenin	R1=H R2=H R3=H R4=OH	Reports on the superior interacting capacity of apigenin over safranal for 5HT1A/5HT2A receptors. Alters brain monoamine levels and serotonin receptor interactions. Additionally, apigenin suppressed the production of proinflammatory cytokines, which may explain its anxiolytic properties.	97, 98
Diosmetin	R1=H R2=H R3=OH R4=OCH_3	Diosmetin had memory-enhancing and anxiolytic-like effects suggestively via GABAA receptor modulation, which likely occurs via their benzodiazepine-binding site. Selective MAO-B inhibitory activity.	99, 100
Flavone C Glucoside			
Rutin	R1=O- sugar moiety R2=H R3=OH R4=H R5=OH R6=OH	Effective in anxiety-like behaviors that are produced by changes in monoamine levels. Aids in the restoration of oxidative/nitrergic, HPA, and neuroinflammatory inhibitions to normal levels.	101, 102
Isorhamnetin	R1=O- sugar moiety R2=H R3=O-sugar moiety R4=H R5=OCH_3 R6=OH	Reported to exhibit remarkable monoamine oxidase. A inhibitory activity.	103
Poly-methoxy flavones			
Nobiletin	R1=H R2=OCH_3 R3=OCH_3	Via inhibition of neuro-inflammation and preventing synaptic damage.	104
Tangeretin	R1=H R2=OCH_3 R3=H	Via activation of nuclear factor erythroid 2-related factor 2 signaling pathway.	105

(Table 2 continued)

(Table 2 continued)

Phytoconstituent	Chemical Structure	Anxiolytic Action	Reference(s)
Other Flavonoids			
Catechin		Mitigates anxiety-related behaviors, via BDNF- and glucocorticoids-mediated signaling. Prevents anxiety-like symptoms brought on by corticosteroids by reducing oxidative stress. Reduces anxiety-like behavior in rats by preventing hippocampal neuroinflammation and apoptosis, and alleviates apoptosis by reversing changes in IL-6 and STAT3 in the brain.	106–108
Myricetin		HPA axis regulation and activation of the BDNF-ERK signaling pathway. Reduces the production of inflammatory indicators, lipid peroxidation, and reactive oxygen species (ROS); it also modifies a number of neurochemicals, such as glutamate, GABA, and serotonin.	109, 110
Caffeic acid		Via indirect modulation of alpha 1A-adrenoceptor system in mice. Causes decrease in the hippocampal N-methyl-D-aspartate (NMDA) receptor expression, which has anxiolytic-like effects. Anxiolytic effect via monoaminergic and GABAergic system.	111–113
Diosmin		Positive effects of diosmin against cognitive impairments, including anxiety, may be mediated through a decline in the TNF-α concentrations in the hippocampus as a pro-inflammatory cytokine.	114
Phenolic Acids			
Chlorogenic acid		Via activation of the benzodiazepine receptor in mouse causes activation of the BDNF-tropomyosin-related kinase B (TrkB) signaling pathway in rat hippocampal regions leading to anti-anxiety effects.	115, 116
Ferulic acid		Reduces symptoms of anxiety and depression by controlling microbial metabolism and the gut microbiota. Also, via mitigation of N-methyl-D-aspartate (NMDA) receptors in mice.	117, 118
Sinapic acid		Anxiolytic effects via GABA(A) receptors as reported for a study in mice.	119, 120

(Table 2 continued)

(Table 2 continued)

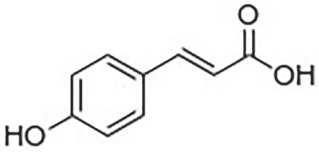
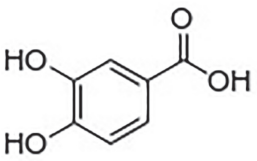
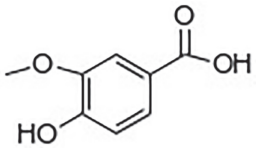
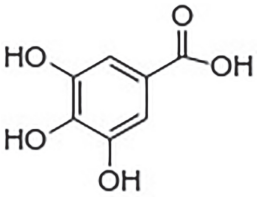
Phytoconstituent	Chemical Structure	Anxiolytic Action	Reference(s)
p-coumaric acid		GABAergic activity in rats. Increases hippocampus neurogenesis, enhances cognitive performance, and lowers anxiety in post-ischemic stroke mice by activating the BDNF/TrkB/AKT signaling pathway.	121, 122
Protocatechuic acid		Via action on the serotonergic nervous system and monoamines in rats. Ability to regulate the antioxidant defense system and oxidative damage in the hippocampal and cerebral cortex of mice, thereby maintaining pro- and anti-oxidative equilibrium.	89, 123
Vanillic acid		Decreases inflammatory responses and exert anxiolytic action via Akt signaling activation in rat models.	124
Gallic acid		Anxiolytic action via activation of AMP-activated protein kinase.	125

Table 3. List of Government-Sponsored Clinical Trials Related to Anxiety in Citrus Species.

Clinical Trial No.	Citrus Species	Trial Name	Trial Type	Trial Phase	Publication Reference (If Any)
NCT00097253	*Citrus limonum*	Psychoneuroimmunology and mind–body medicine: olfaction, mood, and physiological responses.	Interventional	I	Not published
NCT03583801	*Citrus sinensis* L. Persoon, *Citrus reticulata* blanco	Assessment of the aromatherapy to alleviate peri-operative anxiety in ambulatory elective upper limb surgery under loco-regional anesthesia (AROMA).	Interventional, randomized, open-label	Not applicable	Not published
NCT03090750	*Citrus bergamia*	Effects of aromatherapy on anxiety in invasive radiologic procedure.	Interventional, randomized, open-label	I	Not published
NCT04495842	Blends of Citrus essential oils (species not mentioned)	The effect of aromatherapy on COVID-19-induced anxiety.	Interventional, randomized	Not applicable	Not published
NCT06072859	*Citrus forest*	The impact of simulated forest immersion therapy on pain and anxiety in patients axial spondyloarthritis (axSpA).	Interventional, randomized	Not applicable	Not published

*The details of the trials can be found at the official website (ClinicalTrials.gov) of U.S. Department of Health and Human Services, National Institutes of Health, National Library of Medicine and National Centre for Biotechnology Information.

Table 4. List of Clinical Trials Reported in the Literature (2014–2024) Related to Anxiety from Citrus Species.

Citrus Species	Trial Type	Trial Outcome	Reference (If Any)
C. aurantium	Randomized, controlled, triple-blind clinical trial	The study found that bitter orange significantly reduced the mean trait-anxiety scores in postmenopausal women compared to the control group.	126
C. aurantium	Controlled, randomized, two-center study	Anxiety and fatigue scores of patients with acute myocardial infarction were statistically significantly compared to control group after inhalation of three drops of *Citrus aurantium* essential oil (or a placebo) in an oxygen mask for 20 minutes.	127
C. aurantium	Placebo-controlled double-blind trial	A study involving 140 acute coronary syndrome patients found that inhalation aromatherapy, specifically *Citrus aurantium* L. fragrance, significantly reduced anxiety levels after two days of hospital admission.	128
C. aurantium	Placebo-controlled randomized trial	Patients in intensive care units were given *Citrus aurantium* inhalational aromatherapy for 30 minutes, leading to significantly lower anxiety levels within three hours and immediately after.	129
C. aurantium	Randomized, single-blind-controlled trial	Patients before coronary angiography were inhaled with *Citrus aurantium* essential oil, while a control group received distilled water. Vital indicators and Spielberger's STAI were measured, showing significant decrease in anxiety and stress levels.	39
C. aurantium	A placebo-controlled, single-blind, randomized clinical trial	Ninety patients undergoing surgery were divided into two groups: intervention (spring orange) and control. Men showed no acute anxiety after 20 minutes of orange aroma therapy.	130
C. limon	Clinical, multi-center, blinded assessor trial	Trial involving 100 patients with acute myocardial infarction found that lemon inhalation aromatherapy significantly reduced anxiety, systolic blood pressure, ST-segment and T wave alterations, and heart rate regulation.	131
C. bergamia	A controlled interventional trial	Trial on 60 cholecystectomy patients found that aromatherapy with bergamot orange essence significantly reduced anxiety and salivary alpha amylase levels.	132

Isolated Phytoconstituents from Citrus Species and Theiranxiolytic Effects

The genus *Citrus* is known to have extensive phytochemical findings that highlight the presence of both volatile and non-volatile components in vivid polyphenols, which include phenolic acids, lignans, dihydrochalcones, and flavones, flavanols, and polymethoxy flavones (Figure 2).[74] Citrus fruits are not only high in vitamins C and B but also in minerals and macronutrients such as dietary fibers, carbs, crude proteins, lipids, and phenolic compounds that have significant health benefits.[75] Conversely, EOs derived from citrus species find widespread application in the food and beverage, cosmetic, pharmaceutical, and perfume sectors.[76] Table 2 briefs the anxiolytic *Citrus* phytoconstituents along with their proposed mechanistic actions, and in Tables 3 and 4, vivid clinical trials of *Citrus* species in anxiety have been represented.

Conclusion

There have been several reports of unfavorable and unavoidable side effects from traditional synthetic medications, leading to low patient compliance with treatment regimens.[85] Consequently, as an efficacious treatment for several brain illnesses, herbal medicines are being favored over synthetic pharmacological therapies. About 1300 species are included in the genus *Citrus*; the most widely consumed are *C. limon* (lemon), *C. reticulata* (mandarin), and *C. sinensis* (orange). Although research and development, as well as the commercial use of several citrus varieties, have attracted some interest recently, analyzing neglected citrus species closely can help to improve their processing into well-known anxiolytic leads by revealing their untapped potential. The information on the anxiolytic phytochemical components of the widely used citrus species has been compiled in this review. Furthermore, it emphasizes the extensive exploration of underutilized citrus species, which have a rich bioactive profile and enormous potential in pharmaceutical research and development.

Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; **VO:** Volatile oil; **GABA:** γ-aminobutyric acid; **HT:** Hydroxy tryptamine; **EO:** Essential oil; **Nrf2:** nuclear factor erythroid 2–related factor 2; **ARE:** Antioxidant responsive element; **MAO:** Monoamine oxidase; **BDNF:** Brain-derived neurotrophic factor; **SOD:** Superoxide dismutase; **CAT:** Catalase; **HPA:** Hypothalamus-pituitary-adrenal axis; **iNOS:** Inducible nitric oxide

synthase; **IL:** Interleukin; **STAT3:** Signal transducer and activator of transcription 3; **ROS:** Reactive oxygen species; **NMDA:** N-methyl-D-aspartate; **TNF:** Tissue necrosis factor; **TrkB:** Tropomyosin-related kinase B; **AMP:** Adenosine monophosphate; **COVID:** Coronavirus disease; **axSpA:** Anxiety in Patients Axial Spondyloarthritis.

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Author Contributions

HK did the literature search, triage and initial manuscript drafting as part of her doctoral research work. UK contributed in conceptualization, review, final drafting of the review work. NC contributed in major revisions.

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