

REVIEW ARTICLE



A Review on Phytochemical Characterization and Therapeutic Applications of *Citrus medica*

Ramakrishna S^{*1}, Harshita B Nalawala², Narayana Murthy G³

¹ Assistant Professor, Department of Pharmacognosy, National College of Pharmacy, Shivamogga, Karnataka, India

² UG Scholar, Department of Pharmacognosy, National College of Pharmacy, Shivamogga, Karnataka, India

³ Professor and Principal, Department of Pharmacognosy, National College of Pharmacy, Shivamogga, Karnataka, India

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Abstract: *Citrus medica* L. (Citron), one of the original citrus species, possesses a long history of use in traditional medicine, particularly in India and Southeast Asia. Its characteristic large, fragrant fruit with a thick rind has been employed as a digestive, carminative, and anti-inflammatory remedy. Current research establishes these ethnobotanical uses through detailed phytochemical analysis. The volatile oil profile of the fruit is dominated by components such as Isolimonene (~39.4%), Limonene (~23.1%), and Citral (~21.8%), while the leaf uniquely contains Erucylamide (~28.4%) as a major constituent. Beyond the essential oils, *C. medica* is a rich reservoir of bioactive flavonoids, including Naringin, Naringenin, and polymethoxylated flavones like Didymin. These compounds show significant pharmacological effects. Mechanistic studies indicate these bioactives modulate critical cellular pathways, such as Nrf-2 and MAPK, to counter oxidative stress and inflammation. This activity translates into potent neuroprotective properties relevant to Alzheimer's and Parkinson's diseases, as well as significant anticancer activity against various cell lines, including drug-resistant neuroblastoma. Moreover, its constituents show efficacy in managing metabolic and cardiovascular disorders, along with broad-spectrum antimicrobial and antiviral potential. This combination of traditional knowledge and modern evidence indicates *C. medica* as a valuable source for developing novel nutraceuticals and therapeutic agents for chronic and degenerative conditions.

Keywords: *Citrus medica*; Citron; Phytochemistry; Traditional Medicine; Pharmacological Activity.

1. Introduction

Citrus medica L., commonly known as Citron, is an ancient citrus species believed to have originated in the sub-Himalayan regions of India and Southeast Asia [1]. It is a small, evergreen shrub or tree belonging to the Rutaceae family, notable for its large, fragrant, and distinctively thick-rinded fruit [2]. Taxonomically, it is considered one of the foundational species from which most modern citrus cultivars are derived, alongside the pomelo (*C. maxima*) and the mandarin (*C. reticulata*) [3].

Historically, *C. medica* holds significant cultural and medicinal value. It was the first citrus fruit to be introduced to the Mediterranean region, where it was prized in antiquity for its potent aroma and perceived protective properties [4]. In traditional medicine systems, particularly in Ayurveda and Traditional Chinese Medicine (TCM), various parts of the plant have been utilized for centuries. The fruit, peel, and leaves were commonly prepared to treat digestive ailments, act as a carminative, and alleviate inflammatory conditions [5].



Figure 1. Leaves and Fruits of *Citrus medica*

* Corresponding author: Ramakrishna S

Apart from its medicinal uses, the plant's aromatic properties have secured its role in the cosmetic, perfumery, and food industries. The essential oil, rich in volatile compounds, is a valued ingredient, while the thick peel is often candied or used in culinary preparations [6]. In recent years, scientific investigation has shifted towards validating its ethnobotanical legacy. Modern pharmacological studies are increasingly isolating and characterizing bioactive compounds from *C. medica*, revealing a distinct phytochemical profile. This has led to a surge of interest in its potential as a source for novel therapeutic agents to manage a spectrum of chronic and degenerative diseases [7].

2. Phytochemical Profile

The therapeutic properties of *Citrus medica* are directly attributable to its complex and varied phytochemical composition. Different parts of the plant, including the fruit, peel, leaves, and seeds, contain distinct profiles of bioactive compounds [8]. These can be broadly categorized into volatile constituents, primarily essential oils, and non-volatile compounds, which include a rich assortment of flavonoids, organic acids, vitamins, and other molecules.

2.1. Volatile Constituents

The essential oils are responsible for the characteristic potent fragrance of the citron. Gas chromatography-mass spectrometry (GC-MS) analyses have revealed significant variations in the chemical profiles of oils derived from different parts of the plant.

2.1.1. Fruit Essential Oil

The volatile fraction of the *C. medica* fruit is dominated by monoterpene hydrocarbons. Key compounds identified include Isolimonene, which is often the most abundant component at approximately 39.4%, followed by Limonene (approx. 23.1%) and the aldehyde Citral (approx. 21.8%) [9]. Other minor constituents such as beta-Myrcene, Neryl acetate, and Neryl alcohol contribute to the oil's complex aroma and biological activity [10].

2.1.2. Leaf Essential Oil

The leaf essential oil presents a markedly different chemical signature. Its most abundant constituent is the fatty acid amide, Erucylamide (approx. 28.4%). This is followed by Limonene (approx. 18.4%) and Citral (approx. 13.0%) [9]. The presence of other compounds such as 3,7-dimethyl-2,6-octadien-1-ol acetate and 3,7-dimethyl-6-octenol further differentiates the leaf's profile from that of the fruit [11].

Table 1. Major Phytochemical Constituents of *Citrus medica*

Plant Part	Compound Class	Compound(s)	Significance
Peel (Flavedo)	Essential Oils / Terpenoids	Limonene, Citral, Isolimonene	Comprise over 84% of the essential oil; responsible for aroma and antimicrobial activity.
Leaves	Fatty Acid Amide	Erucylamide	Reported as a major constituent (e.g., ~28%).
Peel & Juice (Albedo)	Flavanones	Naringin, Naringenin, Hesperidin	Key bioactives responsible for anti-inflammatory, neuroprotective, and metabolic effects.
Peel	Polymethoxylated Flavones (PMFs)	Nobiletin, Tangeretin	Highly potent neuroprotective and anticancer agents.
Peel	Flavones	Didymin	Orally active compound studied for targeting drug-resistant neuroblastoma.

2.2. Non-Volatile Bioactive Compounds

Apart from the essential oils, *C. medica* is a significant source of non-volatile secondary metabolites, most notably flavonoids. These phenolic compounds are recognized for their potent antioxidant and biological activities.

2.2.1. Flavonoids

The primary flavonoids identified in *C. medica* include the flavanones Hesperidin and Naringin [12]. Naringin, in particular, and its aglycone, Naringenin, have been the subject of extensive pharmacological investigation [13]. Other citrus flavonoids, including polymethoxylated flavones (PMFs) like Didymin and nobiletin, are also present and contribute to the plant's therapeutic profile [14, 15].

2.2.2. Other Constituents

The fruit pulp and juice are rich in organic acids, primarily Citric acid and Malic acid, which contribute to its sharp taste. The plant is also a well-known source of Vitamin C (ascorbic acid), a potent natural antioxidant [16]. Moreover, the thick rind, or albedo, contains a high percentage of pectin, a soluble fiber with various applications in the food and pharmaceutical industries [17]. Alkaloids, such as Synephrine, have also been reported [18].

3. Ethnomedicinal Applications

The vast phytochemical diversity of *C. medica* shows its wide-ranging use in traditional medicine systems across the globe. Virtually every part of the plant has been employed to prepare remedies for a host of ailments.

The fruit, peel, and juice are most commonly associated with digestive health. The ripe fruit is traditionally considered a stimulant and tonic, used to manage conditions like sore throat, cough, and asthma [19]. The peel, rich in essential oils, is valued as a stimulant and is used to treat dysentery and halitosis [20].

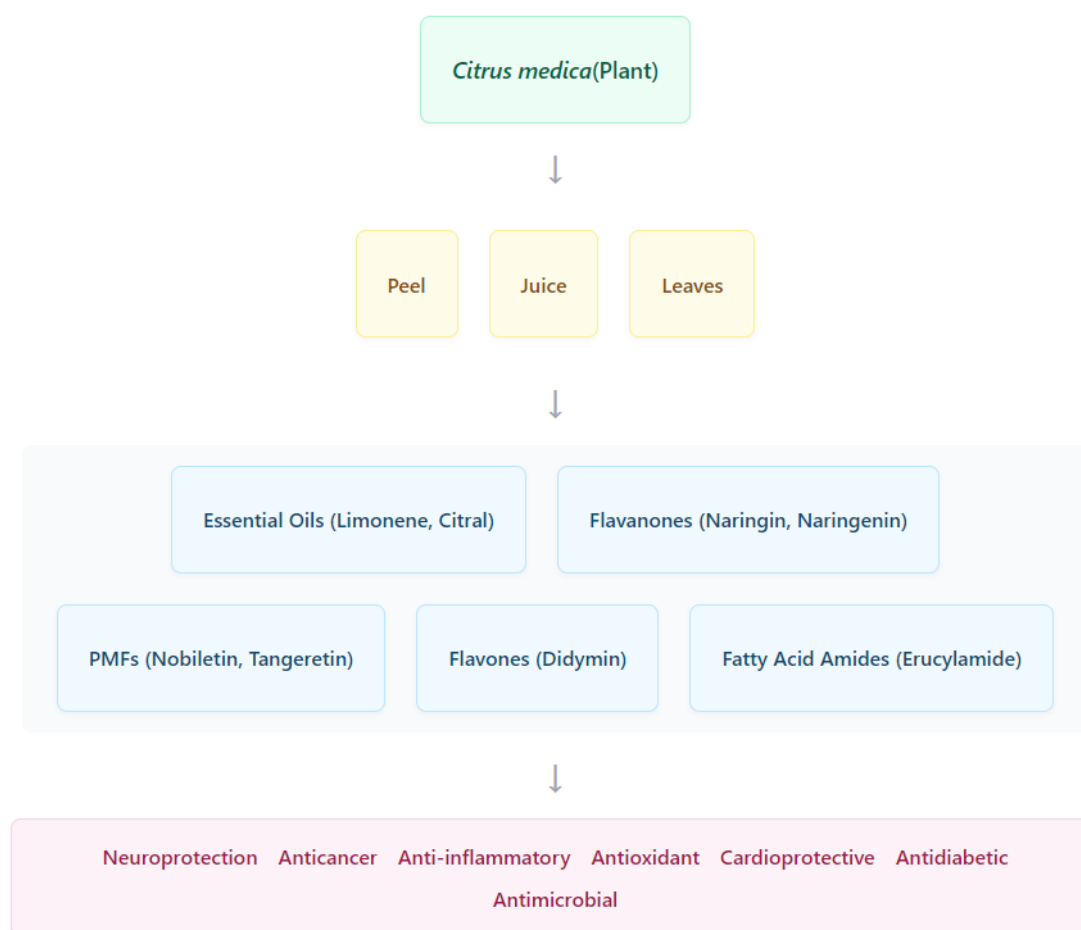


Figure 2. Bioactive Compounds from *Citrus medica* and their Therapeutic Applications

The flowers and leaves also have specific applications. The flowers are traditionally used as an antidepressant, an appetite stimulant, and an astringent. They are also employed in preparations to treat tumors, asthma, and hiccups [21]. The leaves are consumed to address liver-related issues and are used in post-partum anti-spasmodic remedies [22].

The roots and seeds are used for more systemic conditions. The roots are traditionally regarded as anti-parasitic and are used to alleviate constipation, stomachaches, and renal stones [23]. The seeds are considered to have stimulant, tonic, and anti-inflammatory properties, though they are noted as being non-digestive [24]. A decoction of the young shoots or branches is also used to boost appetite and expel intestinal worms [25].

Table 2. Ethnomedicinal Applications of *Citrus medica*

Plant Part Used	Traditional Indication	Reported Therapeutic Action
Root	Renal stones, Constipation, Vomiting, Tumors	Anti-parasitic, Laxative
Flower	Cough, Asthma, Hiccups, Tumors	Astringent, Anti-depressant
Peel (Rind)	Dysentery, Bad breath, Digestive issues	Stimulant, Aromatic, Anti-dysenteric
Ripe Fruit	Sore throat, Cough, Asthma, Leprosy	Tonic, Stimulant, Digestible
Seeds	Inflammation, Tumors	Anti-inflammatory, Stimulant, Tonic
Shoots / Leaves	Intestinal worms, Stomachaches, Liver issues	Appetite stimulant, Anthelmintic, Anti-spasmodic

4. Pharmacological Activities

Modern scientific investigation has begun to rigorously validate the extensive ethnomedicinal uses of *Citrus medica*. The plant's rich reserves of flavonoids, essential oils, and other bioactives are shown to interact with numerous cellular and systemic pathways. Research has demonstrated a wide spectrum of activities, including neuroprotective, anticancer, metabolic, anti-inflammatory, and antimicrobial effects.

4.1. Neuroprotective and Central Nervous System (CNS) Effects

A significant body of research focuses on the potential of citrus-derived compounds to manage complex Central Nervous System (CNS) disorders, including neurodegenerative diseases.

4.1.1. Activity in Neurodegenerative Disorders

The flavonoids from *Citrus* species are a major area of focus for neuroprotection [5]. Compounds such as Naringenin have been identified as promising pharmacological agents for managing progressive conditions like Alzheimer's disease (AD) and Parkinson's disease (PD). The proposed mechanism involves Naringenin's potent antioxidant and anti-inflammatory actions within the brain [10].

This neuroprotective action is linked to the modulation of specific inflammatory and oxidative stress pathways. For instance, citrus bioactives are known to inhibit neuroinflammation by controlling the p38 Mitogen-Activated Protein Kinase (MAPK) pathway and simultaneously activating the Nuclear Factor Erythroid 2-Related Factor 2 (Nrf-2) pathway, which is a master regulator of the body's antioxidant response [16].

4.1.2. Broader CNS Applications

The potential for citrus bioactives extends to other CNS disorders. Polymethoxylated flavones (PMFs), including nobiletin and tangeretin derived from citrus, have shown beneficial effects on cognitive impairment and neural dysfunction in various disorder models [17]. Moreover, the terpene β -caryophyllene, found in citrus and other plants, exhibits neuroprotective, analgesic, and anticonvulsant properties. Its ability to protect the neurovascular unit from oxidative damage and neuroinflammation suggests the blood-brain barrier (BBB) may be a critical target for its therapeutic actions [15]. This is particularly relevant given the link between chronic systemic inflammation, such as in psoriasis, and an increased incidence of neurodegenerative disorders like AD, suggesting a common inflammatory pathology that citrus bioactives may help mitigate [16].

Table 3. Neuroprotective Mechanisms of Citrus-Derived Flavonoids

Condition / Model	Bioactive Compounds	Proposed Protective Mechanism	Reference(s)
Alzheimer's Disease (AD)	Naringenin	Reduces amyloid-beta (A β) toxicity, powerful antioxidant and anti-inflammatory action.	[10]
Parkinson's Disease (PD)	Naringenin	Protects dopaminergic neurons, antioxidant effects.	[10]
Psoriasis-associated NDs	Citrus Bioactives	Inhibits neuroinflammation by controlling p38-MAPK pathway, Activates Nrf-2.	[16]
General CNS Disorders	Polymethoxylated Flavones (PMFs)	Ameliorates cognitive impairment and neural dysfunction.	[17]
Neurological Diseases	Beta-caryophyllene	Neuroprotection, analgesic, potential modulation of blood-brain barrier.	[15]

4.2. Anticancer Properties

Citrus flavonoids have been extensively evaluated for their effects against various malignancies. Their anticancer activity is not due to a single mechanism but rather a pleiotropic effect on multiple signaling pathways that govern cancer cell growth, proliferation, and survival.

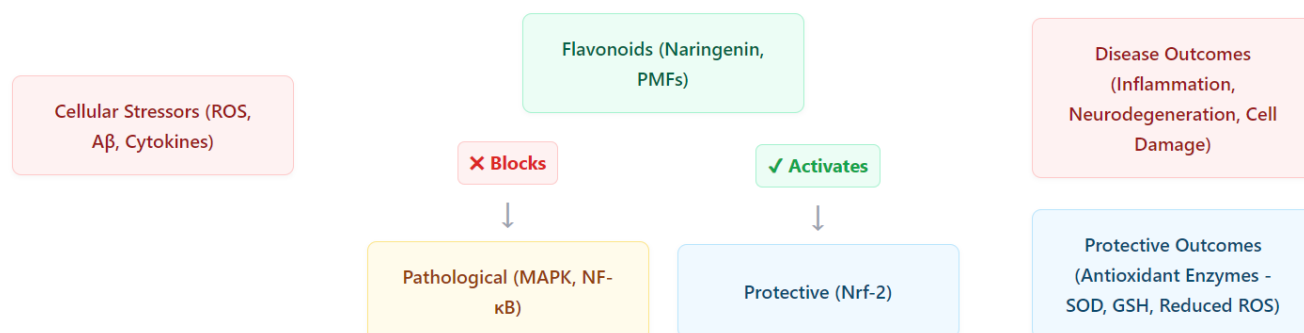


Figure 3. Mechanism of Citrus Flavonoids in Neuroprotection and Anti-inflammation

4.2.1. General Antitumor Mechanisms

The main compounds like Naringin and its aglycone Naringenin are central to these anticancer properties [14]. Their mechanisms include the induction of apoptosis (programmed cell death) and cell cycle arrest, which halts the uncontrolled proliferation of tumor cells [5, 11]. Research into Naringin, for example, shows it can block the tumor cell cycle, prevent invasion and metastasis, and induce autophagy (cellular self-degradation) [8]. These flavonoids also suppress the production of cytokines and growth factors that tumors rely on to develop [14].

4.2.2. Efficacy Against Specific Cancers

This multi-targeted approach has shown efficacy in models of breast, gastric, lung, and liver cancers [5]. In breast cancer, dietary natural products from citrus and other fruits are associated with downregulating the expression of Estrogen Receptor- α , inhibiting proliferation and angiogenesis (the formation of new blood vessels to feed a tumor), and sensitizing tumor cells to radiotherapy and chemotherapy [11].

4.2.3. Overcoming Drug Resistance

Perhaps one of the most promising applications is in overcoming therapeutic resistance. Naringin, for example, has been shown to reverse drug resistance in tumor cells and enhance the sensitivity of conventional chemotherapy drugs [8]. In a striking example, the citrus-derived flavonoid Didymin demonstrated a potent ability to kill treatment-resistant neuroblastoma cells. This effect was achieved in both p53 wild-type and drug-resistant p53-mutant cells. Didymin functions by upregulating the RKIP protein, which in turn inhibits MYCN activation, a key driver in neuroblastoma. This action suggests Didymin could be developed as a safe, oral agent for refractory (treatment-resistant) cancers [19]

Table 4. Anticancer Activity and Targets of Citrus Flavonoids

Cancer Type	Bioactive Compound(s)	Mechanism of Action	Reference(s)
Neuroblastoma (drug-resistant)	Didymin	Induces apoptosis in p53-mutant cells by upregulating RKIP, overcoming drug resistance.	[19]
Breast Cancer	Dietary Flavonoids (incl. Citrus)	Downregulates Estrogen Receptor-alpha (ER- α), induces cell cycle arrest, sensitizes tumors to chemotherapy.	[11]
Various Cancers	Naringin, Naringenin	Inhibits cell proliferation, induces apoptosis, blocks metastasis, modulates cell signaling pathways.	[8, 14]
Gastric Cancer (Progression)	Naringenin, Luteolin	Targets MAPK1 and MAPK3 pathways to improve treatment of chronic atrophic gastritis (a precursor).	[1]

4.3. Metabolic and Cardiovascular Health

The consumption of citrus flavonoids is strongly correlated with improved metabolic and cardiovascular outcomes, positioning them as valuable nutraceuticals for managing conditions like Type 2 Diabetes (T2D) and Cardiovascular Disease (CVD).

4.3.1. Antidiabetic Properties Citrus-derived (poly)phenols may play a role in preventing T2D. Animal studies suggest their beneficial effects are primarily long-term, resulting from sustained consumption rather than acute dosing. The main mechanisms involve the modulation of hepatic glucose metabolism and the improvement of insulin sensitivity in peripheral tissues, rather than a significant effect on initial gut absorption of sugars [7]. However, a notable limitation in many *in vitro* studies is the use of physiologically irrelevant (excessively high) concentrations of these compounds. Future research must address this by using appropriate concentrations and investigating the role of gut microbiota and their catabolites in the bioavailability and action of these polyphenols [7].

4.3.2. Cardiovascular Protection Epidemiological studies link flavonoid-rich food consumption with reduced cardiovascular risk factors and mortality [13]. Citrus flavanones, such as Naringenin, Hesperetin, and Eriodictyol, contribute to this protection through several actions: they scavenge free radicals, enhance glucose tolerance, modulate lipid metabolism, and improve endothelial dysfunction [6]. By suppressing inflammation and inhibiting apoptosis, these compounds help mitigate the progression of conditions like atherosclerosis, which is often a comorbidity of diabetes [6, 13].

4.4. Anti-inflammatory and Oxidative Stress Modulation

A foundational mechanism underpinning many of *C. medica's* therapeutic effects is its potent ability to modulate systemic inflammation and oxidative stress.

4.2.4. Systemic Anti-inflammatory Action

Naringin, for instance, is recognized for its capacity to regulate the body's immune response and maintain immune barrier integrity [12]. It demonstrates broad protective effects that are anti-inflammatory, anti-apoptotic, and anti-ulcerative. Mechanistically, Naringin and other flavonoids regulate systemic inflammation by influencing diverse signaling pathways [12]. This activity is also observed in the treatment of conditions like Chronic Atrophic Gastritis (CAG), where traditional medicine formulations containing citrus bioactives (Naringenin, Luteolin) were found to improve clinical efficacy by targeting key pathways like MAPK1 and MAPK3, which are involved in gastric cancer progression [1].

4.2.5. Response to Oxidative Stress

Naringenin, in particular, has been highlighted as a prophylactic agent for disorders driven by oxidative stress [18]. Its therapeutic value stems from a dual-action mechanism: it directly scavenges Reactive Oxygen Species (ROS) and simultaneously boosts the body's endogenous antioxidant defenses, including enzymes like superoxide dismutase (SOD), catalase, and glutathione (GSH) [18]. This potent antioxidant activity is also the basis for its nephroprotective effects. Naringin has been shown to protect against kidney dysfunction by activating the Nrf-2 signaling pathway, inhibiting apoptosis, and reducing lipid peroxidation, thereby mitigating oxidative stress-induced renal injury [20].

4.3. Antimicrobial and Antiviral Activity

The volatile compounds and phenolics in *C. medica* also confer broad-spectrum antimicrobial properties.

4.3.1. Antifungal Effects

In response to rising antimicrobial resistance, plant-derived compounds are being heavily investigated. Systematic analysis of extracts against *Candida albicans*, the most common human fungal pathogen, identified citrus extracts (*Citrus latifolia*) as being among the most potent. The antifungal activity is primarily attributed to phenolic compounds, flavonoids (like catechin), and terpenoids [2]. This has practical applications, such as in the development of antibacterial fabrics, where citrus essential oils can be microencapsulated using methods like complex coacervation to create cosmetotextiles with stable, controlled-release antimicrobial properties [9].

4.3.2. Antiviral Potential

Essential oils (EOs) from citrus and other plants have demonstrated significant antiviral activity against respiratory pathogens, including influenza and coronaviruses [3]. The lipophilic nature of these EOs allows them to disrupt viral integrity by causing capsid disintegration and destabilizing the viral envelope, thereby preventing host cell entry. EOs from *Citrus resmi* leaves, for example, were found to be effective against the H5N1 virus. Phytochemicals from citrus were also among those identified as effective against the SARS-associated Coronavirus (SARS-CoV) in cell-based assays [3].

Table 5. Pharmacological Activities and Mechanisms of *Citrus medica* Bioactives

Bioactive Compound(s)	Pharmacological Activity	Primary Mechanistic Targets	Reference(s)
Naringenin, PMFs	Neuroprotection	Modulates MAPK pathways, Activates Nrf-2, Reduces A β toxicity	[5, 10, 16, 17]
Naringin, Naringenin, Didymin	Anticancer	Induces apoptosis, Reverses drug resistance (p53-mutant), Modulates ER- α , Inhibits proliferation	[8, 11, 14, 19]
Naringenin, Hesperetin	Metabolic & Cardiovascular	Improves insulin sensitivity, Modulates hepatic glucose metabolism, Improves endothelial dysfunction	[6, 7, 13]
Naringin, Naringenin	Anti-inflammatory & Antioxidant	Activates Nrf-2, Scavenges ROS, Boosts endogenous antioxidants (SOD, GSH), Inhibits inflammatory cytokines	[1, 12, 18, 20]
Essential Oils (Limonene, Citral)	Antimicrobial	Disrupts fungal/viral envelopes, Inhibits <i>C. albicans</i>	[2, 3, 9]

4.4. Other Reported Activities

The diverse applications of citrus compounds continue to expand. In herbal medicine, *Citrus aurantium* is recognized among several plants with hypnotic potential, acting on the CNS by influencing serotonergic and GABAergic systems to promote sedation and improve sleep quality [4].

5. Conclusion

The literature for *Citrus medica* and its derived phytochemicals confirms its significant standing as more than a historical ethnomedicinal plant. Its traditional applications, particularly for digestive, respiratory, and inflammatory ailments, are now substantially supported by modern pharmacological investigations. The plant's complex chemistry, rich in essential oils like Limonene and Citral, and a potent arsenal of flavonoids, most notably Naringin, Naringenin, and various polymethoxylated flavones, provides a clear basis for these broad therapeutic effects. Mechanistic studies reveal that these compounds are pleiotropic, modulating fundamental cellular pathways involved in disease. Their ability to regulate oxidative stress via Nrf-2, control inflammation through MAPK pathways, and induce apoptosis and cell cycle arrest in malignant cells is particularly noteworthy. The potential of citrus bioactives to mitigate complex CNS disorders, improve cardiovascular and metabolic health, and even overcome drug resistance in cancers like neuroblastoma highlights their vast therapeutic potential. Using these promising preclinical findings into robust clinical trials is the essential next step to fully exploit the potential of *Citrus medica* derivatives as safe, low-cost, and effective agents in the management of chronic and refractory diseases.

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