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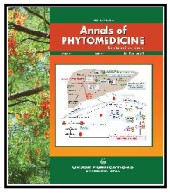

Review Article : Open Access

Ethnopharmacological relevance of *Citrus limon* (L.) Burm. f. as adjuvant therapy

Mohd Ruman Khan, Dinesh Kumar*, Shamim◆, K. Sunand***, Shweta Sharma**** and Geeta Rawat*****

Department of Pharmacy, Rakshpal Bahadur College of Pharmacy, Bareilly-243001, Uttar Pradesh, India
**Atam Institute of Pharmacy, Om Sterling Global University, Hisar-125001, Haryana, India*
***Department of Pharmacy, IIMT College of Medical Sciences, IIMT University, 'O' Pocket Ganga Nagar-250001, Meerut, Uttar Pradesh, India*
****Department of Pharmacology, School of Pharmacy, Anurag University, Medchal-Malkajgiri-500088, Telangana, India*
*****Department of Chemistry, Dr. Akhilesh Das Gupta Institute of Technology and Management, Shastri Park, Shahdara-110053, New Delhi, India*
******Rungta College of Pharmaceutical Sciences and Research, Raipur-490024, Chhattisgarh, India*

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Abstract

Citrus limon (L.) Burm. f. (*C. limon*), commonly known as lemon, is a plant with a rich ethno-pharmacological history and a wide range of bioactive compounds. This review explores the ethnopharmacological relevance of *C. limon* in management of diseases. The use of *C. limon* in traditional medicine systems, such as Ayurveda and Traditional Chinese Medicine, dates back centuries, highlighting its significance as a therapeutic agent. *C. limon* possesses diverse pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anticancer, and hepatoprotective activities, attributed to its various phytochemicals, such as flavonoids, limonoids, coumarins, terpenes, and phenolic compounds. These properties make *C. limon* a promising candidate for complementary or adjuvant therapy alongside conventional treatments. Traditional knowledge and anecdotal evidence have long supported using *C. limon* for various ailments. Modern scientific research has begun elucidating the molecular mechanisms behind its pharmacological effects. Studies have identified bioactive compounds from *C. limon* and investigated their interactions with molecular targets, shedding light on their potential therapeutic applications. The studies have also provided insights into the safety, efficacy, and dosage considerations of *C. limon* based interventions. This comprehensive review analyzes the ethnopharmacological relevance of *C. limon*, including its traditional uses, phytochemical composition, and biological activities. It explores the mechanisms of action of *C. limon* focusing on various disease conditions where *C. limon* has shown promise pharmacological activities. By consolidating the available evidence, this review is a valuable resource for researchers, healthcare professionals, and practitioners seeking to integrate *C. limon* into evidence-based treatment strategies. The findings highlight the potential of *C. limon* as a supportive treatment alongside conventional therapies, contributing to improved patient outcomes and enhanced holistic healthcare approaches. Further research is warranted to fully understand the therapeutic potential and optimize the use of *C. limon* in adjuvant therapy.

1. Introduction

In recent years, there has been a growing interest in exploring the therapeutic potential of natural products as complementary or adjuvant therapies to conventional medical treatments. Medicinal plants play a significant role in traditional systems of medicine, which have been practiced for centuries in various cultures worldwide. These traditional systems of medicine include Ayurveda, Unani medicine, and Indigenous or Native medicine (Gautam, 2022). In ancient India, Ayurveda focuses on achieving balance and harmony in the body, mind, and spirit. Medicinal plants are a fundamental part of Ayurvedic treatments, and herbal remedies are prepared using plant parts such as leaves, roots, bark, flowers, and seeds. Ayurvedic texts categorize herbs based on their properties (taste, energy, and post-digestive effect) and use them to restore health, treat diseases, and promote well-being (Gaurav, 2022; Gaurav *et al*., 2023, 2022). Unani medicine has its roots in ancient Greek medicine and was further developed in the Arab world. It focuses on the balance of the four humors-blood, phlegm, yellow bile, and black bile-to maintain health. Medicinal plants, known as "herbs" in Unani medicine, restore the balance of humor. The Unani system also incorporates elements of Greek, Persian, and Indian traditional medicine (Gautam *et al*., 2021; Khan *et al*., 2022). Indigenous or Native medicine refers to the traditional healing practices of indigenous communities in different parts of the world. These practices are deeply rooted in the cultural and spiritual beliefs of the communities. Medicinal plants are often central to their healing methods, and the knowledge of plant-based remedies is passed down through generations. Indigenous medicine emphasizes the interconnectedness of humans with nature and the significance of maintaining harmony with the environment (Kiran *et*

Corresponding author: Mr. Shamim
Department of Pharmacy, IIMT College of Medical Sciences, IIMT University, 'O' Pocket Ganga Nagar-250001, Meerut, Uttar Pradesh, India
E-mail: pharmacistshamim1@gmail.com
Tel.: +91-9506696061

al., 2021; Mehrotra, 2020; Venkatachalam *et al*., 2021; Zahiruddin *et al*., 2021).

In all these traditional systems of medicine, medicinal plants are chosen based on their therapeutic properties, which have been observed and documented through generations of experience. These plants are used in various forms, such as decoctions, infusions, powders, pastes, oils, and ointments. However, it is essential to note that while these traditional systems of medicine have a long history, their efficacy and safety may vary for different conditions, and scientific research is continually exploring their potential benefits (Dhama *et al*., 2022; Salar *et al*., 2022; Uddin and Veeresh, 2020).

C. limon, plays a pivotal role in both Ayurveda and Unani systems of traditional medicine. In Ayurveda, lemon is considered a potent source of vitamin C and antioxidants, promoting digestion, detoxification, and immune health. It is sour taste is thought to balance the doshas. Unani medicine utilizes lemon for its cooling properties, aiding in digestive disorders and enhancing liver function. The essential oil is valued in aromatherapy. Both systems harness lemon's therapeutic potential to restore harmony and well-being, showcasing its versatile role in holistic healthcare. Among the vast array of medicinal plants, *C. limon,* commonly known as lemon, has gained significant attention due to its rich ethnopharmacological background and diverse bioactive compounds. The use of *C. limon* in traditional medicine systems, such as Ayurveda, Traditional Chinese Medicine, and indigenous healing practices, dates back centuries, highlighting its significance as a therapeutic agent (Viana *et al*., 2020).

C. limon belongs to the Rutaceae family and is widely cultivated for its fruit, renowned for its refreshing taste and high vitamin C content. Beyond its culinary applications, *C. limon* possesses a broad spectrum of pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anticancer, and hepatoprotective activities. These properties can be attributed to the presence of various phytochemicals, such as flavonoids, limonoids, coumarins, terpenes, and phenolic compounds, which have been extensively studied for their beneficial effects on human health (Klimek-szczykutowicz *et al*., 2020). The overview of this medicinal plant is depicted in Figure 1.

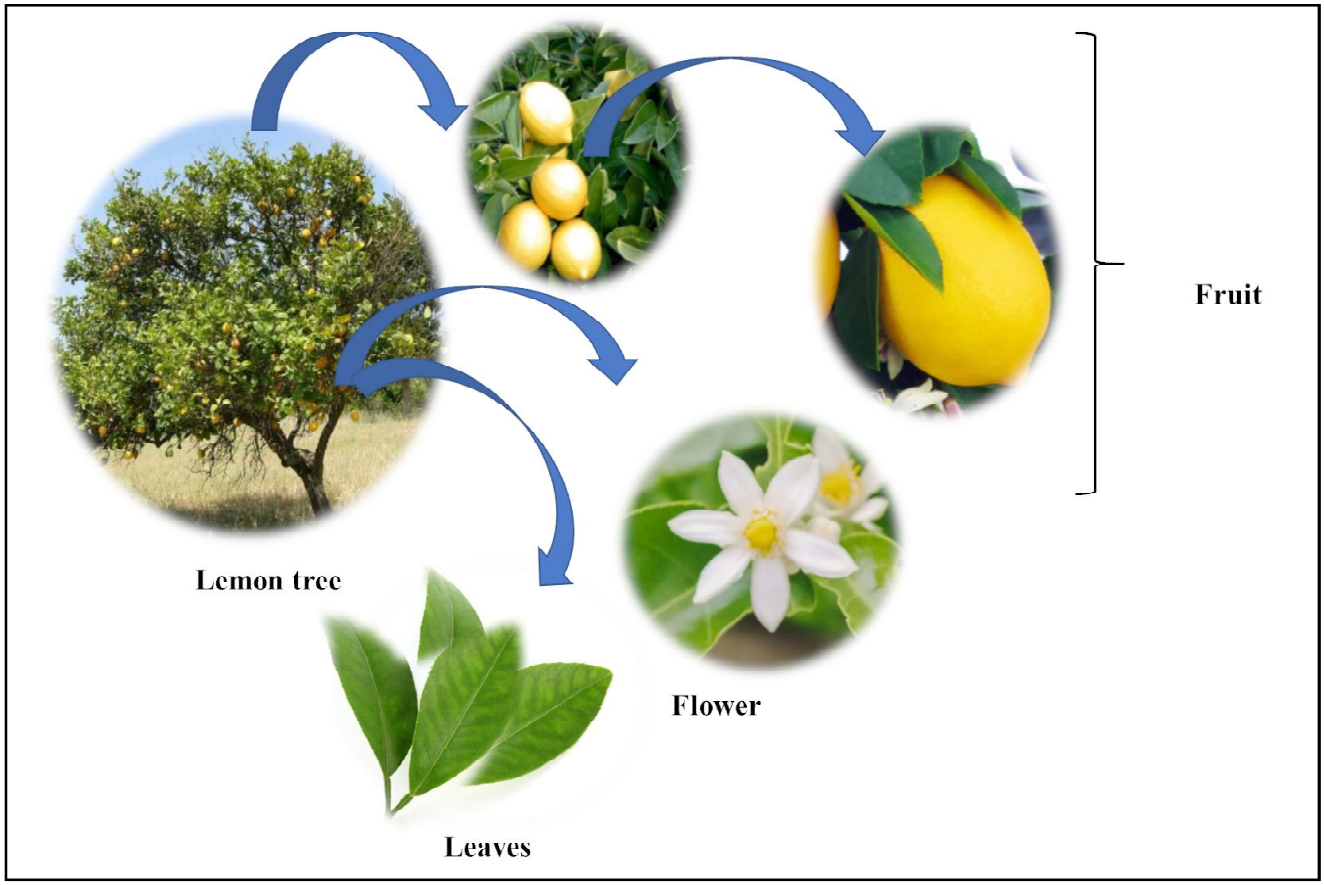

Figure 1: The overview of the medicinal plant C. limon.

2. Ethnopharmacological relevance of *C. limon*

The ethnopharmacological relevance of *C. limon* lies in its traditional use in different cultures to alleviate various ailments. For instance, in traditional Chinese medicine, lemon promotes digestion, relieves cough and phlegm, and enhances the immune system. In Ayurveda, lemon is considered a balancing agent for doshas (energetic principles), and its therapeutic applications range from treating fever and digestive disorders to supporting cardiovascular health. Indigenous communities across the globe have also recognized the medicinal potential of *C. limon,* employing it to address conditions like skin disorders, respiratory ailments, and even mental health issues (Klimek-szczykutowicz *et al*., 2020; Magalhães *et al*., 2023).

While traditional knowledge and anecdotal evidence have long supported the use of *C. limon* as a therapeutic agent, modern scientific research has begun unraveling the molecular mechanisms behind its pharmacological effects. Several studies have identified and isolated bioactive compounds from *C. limon,* investigating their interactions with specific molecular targets and elucidating their potential therapeutic applications. Furthermore, preclinical and clinical studies have shed light on the safety, efficacy, and dosage considerations of *C. limon* based interventions, paving the way for its integration into mainstream healthcare practices (Ashmawy *et al*., 2019; Shaikh *et al*., 2022).

In this review, we aim to comprehensively analyze the ethnopharmacological relevance of *C. limon* as an adjuvant therapy. We will delve into the traditional uses, phytochemical composition, and biological activities of *C. limon,* highlighting its potential as a supportive treatment alongside conventional medicine. Additionally, it explores the therapeutic action and the evidence from preclinical and clinical studies, focusing on various disease conditions where *C. limon* has shown promise. By examining the existing body of knowledge on *C. limon,* this review aims to consolidate the available evidence and contribute to a better understanding of its therapeutic potential. Ultimately, this comprehensive analysis will serve as a valuable resource for researchers, healthcare professionals, and practitioners in their pursuit of integrating *C. limon* into evidence-based treatment strategies, leading to improved patient outcomes and enhanced holistic healthcare approaches (Klimek-szczykutowicz *et al*., 2020).

3. Geographical distribution of *C. limon*

C. limon is native to the regions of Southeast Asia, particularly Northeast India, Myanmar (Burma), and China. Over time, lemon cultivation and trade have spread across various continents, making it one of the world's most widely cultivated and distributed citrus fruits. The origin of *C. limon* is believed to be in Northeast India and Myanmar (Burma). This area is known for its diverse citrus species, and lemon is believed to have been cultivated and selected from wild citrus varieties in this region. From its native range, the cultivation of lemons spread to China and other parts of Southeast Asia. Lemons were likely introduced to China through trade and cultural exchange routes, as citrus fruits have a long history of being valued for their medicinal and culinary properties in traditional Chinese medicine and cuisine. The Arabs are credited with spreading lemons to regions such as Iraq, Iran, and the Levant (Dosoky and Setzer, 2018; González-Molina *et al*., 2010; Klimek-szczykutowicz *et al*., 2020). By the time of the Islamic Golden Age, lemons had become widely cultivated in these regions, and their use as both a culinary ingredient and medicinal remedy became well-established. The introduction of lemons to Europe is believed to have occurred during the period of Islamic rule in regions such as Spain and Sicily. The Moors are believed to have brought lemons to these areas, and their cultivation spread across the Mediterranean (Ashmawy *et al*., 2019; Shaikh *et al*., 2022).

Lemons were likely brought to the Americas by early European explorers and colonists. Their introduction's exact timeline and route need to be well-documented, but they were known to be cultivated in the New World by the 15th and 16th centuries. The favorable climate in regions like Florida and California allowed for successful lemon cultivation, establishing thriving citrus industries in these areas. Currently, *C. limon* is grown in numerous countries around the world. Major lemon-producing countries include India, China, Mexico, Argentina, Spain, the United States, Turkey, and Italy (Klimek-szczykutowicz *et al*., 2020). Within these countries, lemon cultivation is carried out in various regions that provide suitable climatic conditions for citrus cultivation. It thrives in subtropical to tropical climates with warm temperatures and moderate humidity. The optimal temperature range for lemon cultivation is between 20°C to 30°C (68°F to 86°F), and they are sensitive to frost. Lemons require well-drained soils and adequate irrigation to support their growth. Commercial cultivation is primarily focused on producing fresh fruit for consumption, processing into juice and extracts, and for use in various industries, including food, beverage, and cosmetics (Klimek-szczykutowicz *et al*., 2020; Rapisarda *et al*., 2022; Setzer, 2009). It is widely grown in numerous countries worldwide, with large-scale commercial cultivation supporting diverse industries. Lemon's versatility, as both a culinary ingredient and a valuable source of vitamin C, has contributed to its popularity and widespread cultivation across different climatic regions (Ashmawy *et al*., 2019; Shaikh *et al*., 2022). A summary of the geographical distribution of *C. limon* has been summarized in Table 1.

Table 1: Geographical distribution of *C. limon*

Region	Countries and areas
Native range	India, Southeast Asia, and China
Introduced range	Worldwide (widely cultivated)
Major producers	
Mediterranean basin	Spain, Italy, Greece, Turkey, Portugal
North America	United States (California, Arizona, Florida)
South America	Argentina, Brazil
Asia	India, China, Thailand, Vietnam, Pakistan
Africa	Egypt, South Africa, Morocco
Oceania	Australia, New Zealand

4. Phytochemistry of *C. limon*

C. limon, commonly known as lemon, is a citrus fruit that belongs to the Rutaceae family. It is widely cultivated and valued for its culinary and medicinal uses. The chemistry of *C. limon* involves a complex array of natural products, including volatile compounds, flavonoids, limonoids, coumarins, terpenes, and phenolic compounds, which contribute to its characteristic aroma, flavor, and pharmacological properties (Klimek-szczykutowicz *et al*., 2020; Rapisarda *et al*., 2022; Setzer, 2009).

4.1 Volatile compounds

Lemon is renowned for its solid and refreshing aroma, primarily due to the presence of volatile compounds. The major volatile constituents of *C. limon* include limonene, α-pinene, α-terpinene, α-pinene, citral, linalool, and geraniol. These compounds contribute to lemon's characteristic scent and possess antimicrobial and antioxidant activities (Klimek-szczykutowicz *et al*., 2020).

4.2 Flavonoids

Flavonoids are a group of polyphenolic compounds found abundantly in *C. limon*. They include flavones (such as diosmetin and apigenin), flavonols (such as quercetin and kaempferol), flavanones (such as hesperidin and eriocitrin), and their glycosides. Flavonoids exhibit

antioxidant, anti-inflammatory, antiviral, and anticancer properties, contributing to the therapeutic potential of *C. limon*.

4.3 Limonoids

Limonoids are unique triterpenoid compounds found in *C. limon,* known for their bitter taste. They include compounds like limonin, tomlin, backbone, and their derivatives. Limonoids possess various biological activities, including anticancer, antimicrobial, and cholesterol-lowering effects. They also exhibit hepatoprotective properties and have shown promise in preventing and treating certain types of cancer (Dosoky and Setzer, 2018; Klimek-szczykutowicz *et al*., 2020).

4.4 Coumarins

C. limon contains coumarin derivatives, such as umbelliferone, bergapten, and osthol. Coumarins contribute to the characteristic aroma of lemon and possess antioxidant and anti-inflammatory properties. They have also been investigated for their potential anticancer effects (Klimek-szczykutowicz *et al*., 2020).

4.5 Terpenes

Terpenes are a diverse class of compounds found in *C. limon,* contributing to its characteristic flavor and aroma. They include monoterpenes, such as limonene, and sesquiterpenes, such as β-caryophyllene. Limonene, in particular, is a significant constituent of lemon oil and exhibits anticancer, antimicrobial, and anti-inflammatory activities (González-Molina *et al*., 2010; Klimek-szczykutowicz *et al*., 2020).

4.6 Phenolic compounds

C. limon is rich in phenolic compounds, including hydroxycinnamic acids (such as caffeic acid and ferulic acid), flavonoids (mentioned earlier), and coumarins (mentioned earlier). Phenolic compounds contribute to the antioxidant and anti-inflammatory properties of *C. limon* and play a role in its therapeutic potential (González-Molina *et al*., 2010).

5. Pharmacology of *C. limon*

The complex chemistry and abundance of natural products in *C. limon* contribute to its diverse pharmacological properties and traditional medicinal uses. The bioactive compounds in *C. limon* have been extensively studied for their potential health benefits, making it a promising candidate for various applications, including functional foods, nutraceuticals, and natural remedies. Further research is ongoing to explore the full range of natural products and their potential synergistic interactions within *C. limon,* as well as their mechanisms of action and therapeutic applications. *C. limon* possesses a diverse range of pharmacological properties attributed to its various bioactive compounds. The pharmacology of *C. limon* is multifaceted and encompasses antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anticancer, hepatoprotective, cardioprotective, neuroprotective, and dermatological activities, among others (Klimek-szczykutowicz *et al*., 2020). The Pharmacological activities and mechanisms of action of *C. limon* have been summarized in Table 2.

Table 2: Pharmacological activities and mechanisms of action of *C. limon*

S. No.	Pharmacological activity	Mechanism of action	References
1.	Antioxidant activity	Lemons are rich in vitamin C (ascorbic acid) and flavonoids, such as hesperidin and naringenin. These compounds act as potent antioxidants, scavenging free radicals and reducing oxidative stress in the body.	Magalhães *et al*., 2023
2.	Anti-inflammatory activity	Lemon contains bioactive compounds that can inhibit inflammatory pathways, including the production of pro-inflammatory mediators like cytokines and prostaglandins.	Klimek-szczykutowicz *et al*., 2020
3.	Antibacterial activity	Lemons contain various compounds, including limonoids and flavonoids, which possess antibacterial properties. These compounds may help inhibit the growth of certain bacteria.	Klimek-szczykutowicz *et al*., 2020
4.	Hypolipidemic activity	Specific components of lemon, such as flavonoids and polyphenols, may help reduce cholesterol levels and improve lipid profiles by inhibiting cholesterol synthesis or promoting its excretion.	Bhavsar *et al*., 2007
5.	Gastroprotective activity	Lemon is believed to possess gastroprotective properties by protecting the gastric mucosa and reducing the formation of stomach ulcers. Flavonoids and antioxidants present in lemon may contribute to this effect.	Klimek-szczykutowicz *et al*., 2020
6.	Antidiabetic activity	Lemon consumption has been associated with improved insulin sensitivity and glucose metabolism, possibly due to bioactive compounds with beneficial effects on blood sugar levels.	Hartati *et al*., 2021
7.	Anticancer activity	Lemon contains bioactive compounds such as limonoids and flavonoids, which may exhibit chemopreventive effects by inhibiting tumor growth and inducing apoptosis (cell death) in cancer cells.	Hartati *et al*., 2021

8.	Skin brightening	Lemon contains natural citric acid, which has mild exfoliating properties. It can help remove dead skin cells and promote a brighter complexion. The vitamin C in lemon also inhibits melanin production, leading to skin-lightening effects. However, directly applying lemon juice to the skin can irritate, so diluting it or using commercial products with controlled concentrations is recommended.	Shukr and Metwally, 2013
9.	Antimicrobial	The antimicrobial properties of lemon can help combat certain bacteria and fungi on the skin, making it beneficial for mild skin infections or acne-prone skin. However, lemon juice should be used cautiously, as it may be too acidic for some skin types and cause irritation or worsen existing skin conditions.	Klimek-szczykutowicz *et al*., 2020
10.	Astringent	Lemon juice can act as an astringent, helping to tighten and tone the skin. This can be beneficial for reducing the appearance of enlarged pores and controlling excess oil production. However, excessive use can lead to dryness and irritation.	Cox-Georgian *et al*., 2019; Thilagamani and Surya, 2021
11.	Wound healing	Lemon's vitamin C content can support collagen synthesis, essential for wound healing. However, lemon juice should not be applied directly to open wounds, as it may cause stinging and irritation.	Oguwike, 2013; Pazyar *et al*., 2014
12.	Skin conditioning	Lemon extract or oil is sometimes used in skincare products as a skin conditioning agent, providing hydration and nourishment.	Parham *et al*., 2020; Pazyar *et al*., 2014

5.1 Antioxidant activity

C. limon exhibits potent antioxidant properties, primarily due to flavonoids, limonoids, and phenolic compounds. These compounds scavenge free radicals, reduce oxidative stress, and protect cells from oxidative damage. The antioxidant activity of *C. limon* contributes to its potential in preventing or managing various chronic diseases, including cardiovascular disorders, neurodegenerative diseases, and cancer. *C. limon,* commonly known as lemon, is renowned for its potent antioxidant activity, which plays a crucial role in its therapeutic potential. The antioxidant properties of *C. limon* are attributed to the presence of various bioactive compounds, including flavonoids, limonoids, coumarins, phenolic compounds, and vitamin C. These antioxidants help neutralize harmful free radicals, reduce oxidative stress, and protect cells from oxidative damage. Here, we delve into the details of the antioxidant activity of *C. limon* (Klimek-szczykutowicz *et al*., 2020).

C. limon is rich in flavonoids, including flavones (such as diosmetin and apigenin), flavonols (such as quercetin and kaempferol), and flavanones (such as hesperidin and eriocitrin). Flavonoids exhibit potent antioxidant properties by scavenging free radicals, inhibiting lipid peroxidation, and chelating metal ions involved in oxidative processes. These actions contribute to the overall antioxidant capacity of *C. limon*. Limonoids, such as limonin and tomlin, are triterpenoid compounds found in *C. limon*. They possess significant antioxidant activity and contribute to the total antioxidant capacity of the fruit. Limonoids scavenge free radicals, inhibit oxidative enzymes, and enhance antioxidant defenses within the body. Their antioxidant effects are attributed to their ability to quench reactive oxygen species (ROS) and reduce oxidative damage (Dosoky and Setzer, 2018; González-Molina *et al*., 2010; Klimek-szczykutowicz *et al*., 2020).

C. limon contains coumarin derivatives, such as umbelliferone, bergapten, and osthol, which exhibit antioxidant activity. Coumarins act as free radical scavengers and metal chelators, reducing oxidative stress and preventing cellular damage. Their antioxidant properties contribute to the overall protective effects of *C. limon* against oxidative stress-related diseases. *C. limon* is rich in phenolic compounds, including hydroxycinnamic acids (caffeic acid and ferulic acid), exhibiting potent antioxidant activity. Phenolic compounds act as free radical scavengers, inhibit lipid peroxidation, and protect against DNA damage caused by oxidative stress. These compounds contribute significantly to the overall antioxidant capacity of *C. limon*. *C. limon* is well-known for its high vitamin C content. As a potent water-soluble antioxidant, vitamin C plays a vital role in scavenging free radicals, regenerating other antioxidants (such as vitamin E), and protecting cells from oxidative damage. Vitamin C contributes to the antioxidant defense system of the body and enhances the overall antioxidant activity of *C. limon* (González-Molina *et al*., 2010; Klimek-szczykutowicz *et al*., 2020).

Furthermore, the combined action of these antioxidants in *C. limon* provides a robust defense against oxidative stress and its associated health conditions. The antioxidant activity of *C. limon* offers numerous benefits, including protection against oxidative damage: Antioxidants in *C. limon* help prevent cellular damage caused by oxidative stress, reducing the risk of chronic diseases such as cardiovascular disorders, neurodegenerative diseases, and cancer. The antioxidant properties of *C. limon* help combat oxidative stress-induced aging by reducing the damage caused by free radicals to skin cells and supporting collagen production. Antioxidants in *C. limon,* including vitamin C, help strengthen the immune system by protecting immune cells from oxidative damage and promoting their optimal function. The antioxidant activity of *C. limon* contributes to its dermatological applications, including its ability to protect the skin from oxidative stress, reduce inflammation, and promote skin rejuvenation (González-Mas *et al*., 2019; González-Molina *et al*., 2010; Hartati *et al*., 2021; Klimek-szczykutowicz *et al*., 2020).

5.2 Anti-inflammatory activity

The bioactive constituents of *C. limon,* such as flavonoids, limonoids, and coumarins, possess significant anti-inflammatory effects. They

inhibit pro-inflammatory enzymes, such as cyclooxygenases (COX) and lipoxygenases (LOX), and modulate inflammatory mediators, including cytokines and chemokines. *C. limon's* anti-inflammatory activity has been investigated in conditions like arthritis, asthma, and inflammatory bowel disease. *C. limon,* commonly known as lemon, exhibits significant anti-inflammatory activity, contributing to its therapeutic potential. The anti-inflammatory properties of *C. limon* are attributed to its diverse bioactive compounds, including flavonoids, coumarins, and phenolic compounds. These compounds work together to modulate inflammatory pathways, inhibit pro-inflammatory enzymes, and reduce the production of inflammatory mediators. Here, we explore the anti-inflammatory activity of *C. limon* in detail (Hartati *et al*., 2021; Klimek-szczykutowicz *et al*., 2020).

C. limon contains various flavonoids, such as diosmetin, apigenin, quercetin, and kaempferol, which exhibit potent anti-inflammatory effects. Flavonoids inhibit the activity of pro-inflammatory enzymes, such as cyclooxygenase (COX) and lipoxygenase (LOX), thereby reducing the synthesis of inflammatory mediators like prostaglandins and leukotrienes. Additionally, flavonoids modulate signaling pathways involved in inflammation, such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), leading to decreased expression of inflammatory genes. Limonoids in *C. limon,* such as limonin and tomlin, demonstrate anti-inflammatory activity. They inhibit the release of pro-inflammatory cytokines from immune cells, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6(IL-6). Limonoids also suppress the activation of NF-κB, a key transcription factor involved in the inflammatory response. By modulating these inflammatory pathways, limonoids contribute to the anti-inflammatory activity of *C. limon*. It contains coumarin derivatives, including umbelliferone, bergapten, and osthol, which possess anti-inflammatory properties. Coumarins inhibit the activity of pro-inflammatory enzymes and reduce the production of inflammatory mediators, such as prostaglandins and leukotrienes. Furthermore, they inhibit the activation of immune cells involved in inflammation, such as macrophages and neutrophils. Phenolic compounds present in *C. limon,* including hydroxycinnamic acids (*e.g.,* caffeic acid, ferulic acid), contribute to its anti-inflammatory activity. These compounds inhibit the release of pro-inflammatory cytokines and chemokines from immune cells. Phenolic compounds also act as scavengers of free radicals, reducing oxidative stress, which can contribute to chronic inflammation (González-Molina *et al*., 2010; Hartati *et al*., 2021; Klimek-szczykutowicz *et al*., 2020; Liu *et al*., 2022).

5.3 Antimicrobial activity

C. limon, commonly known as lemon, possesses notable antimicrobial activity, making it a valuable natural agent against various bacterial, fungal, and viral pathogens. The antimicrobial properties of *C. limon* can be attributed to its bioactive compounds, including limonene, citral, and other volatile components found in its essential oil. Here, we explore the antimicrobial activity of *C. limon* in detail (Klimek-szczykutowicz *et al*., 2020).

5.3.1 Bacterial activity

The essential oil derived from *C. limon* exhibits significant antibacterial effects against many bacteria, including gram-positive and gram-negative strains. The antimicrobial action is attributed to compounds such as limonene and citral, which disrupt the bacterial cell membrane, inhibit bacterial enzymes, and interfere with essential metabolic processes. *C. limon* is effective against pathogens like *Escherichia coli*, *Staphylococcus aureus*, *Salmonella* spp., and *Pseudomonas aeruginosa* (Klimek-szczykutowicz *et al*., 2020).

5.3.2 Fungal activity

C. limon demonstrates antifungal properties against various fungal pathogens, including *Candida* spp. and *Aspergillus* spp. The essential oil components of *C. limon* can inhibit fungal growth by disrupting the fungal cell membrane, inhibiting fungal enzymes, and interfering with fungal metabolic processes. Lemon extract has been used as a natural remedy for fungal skin infections and candidiasis.

5.3.3 Viral activity

C. limon exhibits antiviral activity against specific viral pathogens. The essential oil components, particularly limonene and citral, have been shown to inhibit the replication of certain viruses, including herpes simplex virus (HSV) and human immunodeficiency virus (HIV). However, further research is needed to fully elucidate the mechanisms of action and potential applications against viral infections. The antimicrobial properties of *C. limon* make it useful for food preservation. Lemon extracts or essential oil can be applied as natural preservatives, inhibiting the growth of spoilage-causing bacteria and fungi in food products. *C. limon's* antimicrobial effects are beneficial for oral health. Lemon extracts or essential oil can be used in mouthwashes or dental products to combat oral pathogens and reduce the risk of oral infections. *C. limon* has been used in traditional medicine for wound care due to its antimicrobial properties. It can be used topically to prevent infection and promote wound healing. The antimicrobial activity of *C. limon* makes it suitable for surface disinfection in household and healthcare settings. Lemon-based cleaning products can help eliminate harmful bacteria and fungi from surfaces (González-Molina *et al*., 2010; Hartati *et al*., 2021; Klimek-szczykutowicz *et al*., 2020; Rapisarda *et al*., 2022; Setzer, 2009).

Furthermore, it has been suggested that lemon contains bioactive compounds, including limonoids and flavonoids, which may have the ability to disrupt the lipid envelopes of certain viruses. Viral envelopes are essential for the virus to enter host cells and replicate. By interfering with these envelopes, lemon compounds could inhibit viral entry and replication. Lemon is rich in vitamin C, which is known to support the immune system. A robust immune response is crucial for the body to fight off viral infections effectively. Vitamin C may enhance the function of various immune cells, helping the body's defense mechanisms combat viral invaders. Lemon's antioxidant compounds, such as vitamin C and flavonoids, can scavenge free radicals and reduce oxidative stress. During viral infections, the body's immune response can produce reactive oxygen species (ROS), contributing to tissue damage. Lemon's antioxidants may help mitigate this oxidative damage and support the body's ability to deal with viral infections (Curini *et al*., 2005; Muralidass *et al*., 2021; Mir *et al*., 2016; Muralidass and Devi, 2021).

Some studies suggest that lemon compounds may interfere with viral replication processes. For example, certain flavonoids have been shown to inhibit the activity of viral enzymes crucial for viral replication. Lemon extracts have demonstrated direct inactivation of some viral particles. This action might involve interactions between lemon compounds and the viral surface proteins, rendering the virus unable to infect host cells.

5.4 Antidiabetic activity

C. limon, commonly known as lemon, possesses potential antidiabetic activity, making it a promising natural agent in managing diabetes mellitus. The antidiabetic properties of *C. limon* are attributed to its bioactive compounds, including flavonoids, limonoids, and phenolic compounds, which contribute to its therapeutic effects. Here, we explore the antidiabetic activity of *C. limon* in detail. *C. limon* has been shown to enhance glucose metabolism, leading to improved glycemic control. The bioactive compounds in *C. limon* may promote glucose uptake by cells and increase insulin sensitivity, thereby assisting in regulating blood glucose levels. This effect mainly benefits individuals with type 2 diabetes who experience insulin resistance.

C. limon contains bioactive compounds that inhibit carbohydrate-digesting enzymes, such as α-amylase and α-glucosidase. These enzymes break down complex carbohydrates into simple sugars, which are absorbed into the bloodstream. By inhibiting these enzymes, *C. limon* can slow down the digestion and absorption of carbohydrates, leading to a more gradual release of glucose into the bloodstream and preventing sudden spikes in blood sugar levels. Oxidative stress plays a significant role in the development and progression of diabetes. *C. lemon* is rich in antioxidants, such as flavonoids and phenolic compounds, which can counteract oxidative stress and reduce cellular damage caused by reactive oxygen species (ROS). By reducing oxidative stress, *C. limon* may help protect pancreatic beta cells, improve insulin secretion, and preserve insulin sensitivity (Dosoky and Setzer, 2018; González-Molina *et al*., 2010; Klimek-szczykutowicz *et al*., 2020). Chronic low-grade inflammation is associated with insulin resistance and impaired glucose metabolism in diabetes. *C. limon* possesses anti-inflammatory properties attributed to its bioactive compounds. By modulating inflammatory pathways and reducing the production of pro-inflammatory cytokines, *C. limon* may help improve insulin sensitivity and glucose metabolism. *C. limon* may help regulate blood glucose levels and improve glycemic control in individuals with diabetes. Consuming *C. limon* as part of a balanced diet may prevent type 2 diabetes by supporting healthy glucose metabolism and insulin sensitivity. The antioxidant and anti-inflammatory effects of *C. limon* may have protective effects against diabetic complications, such as cardiovascular diseases and diabetic neuropathy (González-Molina *et al*., 2010; Hartati *et al*., 2021; Klimek-szczykutowicz *et al*., 2020; Rapisarda *et al*., 2022; Setzer, 2009).

5.5 Anticancer activity

C. limon, commonly known as Lemon, exhibits potential anticancer activity, making it a subject of interest in cancer research. The anticancer properties of *C. limon* are attributed to its bioactive compounds, including limonoids, flavonoids, and phenolic compounds, which contribute to its therapeutic effects. Here, we explore the anticancer activity of *C. limon* in detail. It contains limonoids, such as limonin and Tomlin, showing promising anticancer results. Limonoids inhibit the growth and proliferation of cancer cells by inducing cell cycle arrest, promoting apoptosis (programmed cell death), and suppressing tumor cell invasion and metastasis. They also exhibit antioxidant properties, reducing oxidative stress and cellular damage associated with cancer development. It is rich in flavonoids, such as hesperidin and diosmetin, demonstrating anticancer potential. Flavonoids exert their anticancer effects through various mechanisms, including antioxidant activity, cancer cell proliferation inhibition, apoptosis induction, and modulation of signaling pathways involved in tumor growth and progression. They have shown efficacy against various cancer types, including breast, colon, lung, and prostate cancer (Ashmawy *et al*., 2019; Shaikh *et al*., 2022).

Phenolic compounds in *C. limon,* such as caffeic acid and ferulic acid, exhibit potential anticancer properties. These compounds possess antioxidant and anti-inflammatory effects, contributing to their anticancer activity. They can inhibit cancer cell proliferation, induce apoptosis, and interfere with tumor angiogenesis (the formation of blood vessels to support tumor growth). *C. limon* has been shown to modulate immune responses, which play a crucial role in cancer surveillance and elimination. Components of *C. limon* have been found to enhance immune cell function, such as natural killer (NK) cells and lymphocytes, thereby promoting an effective immune response against cancer cells. The anticancer activity of *C. limon* offers several potential benefits, such as the bioactive compounds in *C. limon* may help prevent the initiation and progression of cancer by inhibiting tumor growth, inducing cancer cell death, and protecting against DNA damage caused by oxidative stress. *C. limon* anticancer properties make it a potential adjuvant therapy alongside conventional cancer treatments, such as chemotherapy and radiation therapy. It may enhance treatment efficacy, reduce side effects, and improve treatment outcomes. *C. limon's* bioactive compounds, particularly limonoids, and flavonoids, have shown chemopreventive effects, reducing the risk of cancer development in individuals at high risk or with pre-cancerous conditions (Aazza *et al*., 2014).

5.6 Hepatoprotective activity

C. limon has hepatoprotective properties and has been investigated for its potential in liver health. It helps protect the liver against toxic substances, oxidative stress, and inflammation. *C. limon* exerts its hepatoprotective effects by enhancing antioxidant defenses, reducing lipid peroxidation, and modulating liver enzymes involved in detoxification (Bhavsar *et al*., 2007).

5.7 Cardioprotective activity

C. limon, commonly known as Lemon, possesses significant cardioprotective activity, making it beneficial for cardiovascular health. The cardioprotective properties of *C. limon* are attributed to its bioactive compounds, including flavonoids, limonoids, and phenolic compounds. *C. limon* exhibits antioxidant effects, reducing oxidative stress and preventing damage to cardiac cells and blood vessels. The bioactive compounds in *C. limon* scavenge free radicals, inhibit lipid peroxidation, and enhance endogenous antioxidant defenses. Furthermore, *C. limon* helps improve lipid profile by reducing total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels. It also enhances high-density lipoprotein (HDL) cholesterol levels, promoting a healthier lipid balance. *C. limon* exhibits antiplatelet and antithrombotic properties, inhibiting platelet aggregation and reducing the risk of blood clot formation. This effect is attributed to compounds like hesperidin and diosmin in *C. limon*. Additionally, *C. limon* promotes vasodilation, improving blood flow and reducing hypertension. The flavonoids in *C. limon* enhance nitric oxide production, a molecule that helps relax blood vessels and maintain healthy blood pressure levels (Krishna *et al*., 2017).

The combined effects of these mechanisms contribute to the cardioprotective activity of *C. limon,* reducing the risk of cardiovascular disorders such as hypertension, atherosclerosis, and ischemic heart disease. Incorporating *C. limon* into a balanced diet or using it as a natural remedy may support cardiovascular health and provide protective effects against cardiovascular diseases. However, consulting healthcare professionals for personalized advice and integrating *C. limon* into a comprehensive cardiovascular health plan is essential. Neuroprotective activity: Some bioactive compounds in *C. limon* exhibit neuroprotective effects and have been studied for their potential in neurodegenerative disorders. These compounds protect neurons against oxidative damage, reduce neuroinflammation, and modulate neurotransmitter systems. *C. limnos* neuroprotective activity may have implications for conditions such as Alzheimer's disease and Parkinson's disease (Ademosun *et al*., 2019; Dharmago *et al*., 2017; Sm *et al.*, 2019).

5.8 Dermatological activity

C. limon, commonly known as Lemon, exhibits dermatological activity and offers several benefits for skin health. The bioactive compounds present in *C. limon,* including flavonoids, limonoids, and vitamin C, contribute to its dermatological properties. *C. limon* possesses antimicrobial activity, making it effective against acne-causing bacteria. Lemon extract or juice can be used topically to cleanse the skin, reduce excess oil production, and help control acne breakouts. The antioxidant properties of *C. limon* help protect the skin against oxidative stress and damage caused by free radicals. This can contribute to the prevention of premature aging, such as fine lines, wrinkles, and age spots. The high vitamin C content in *C. limon* supports collagen production, improving skin elasticity and firmness. *C. limon* is also known for its skin-brightening effects. The natural acids present in lemon can help exfoliate the skin, remove dead skin cells, and promote a more radiant complexion. However, caution should be exercised as lemon juice may cause sensitivity or irritation in some individuals. Doing a patch test and diluting lemon juice before applying it to the skin is advisable. Moreover, *C. lemon* has been used in traditional medicine for wound healing. Its antimicrobial properties help protect against infections, and its antioxidant activity aids tissue repair and regeneration. While *C. limon* offers potential benefits for skin health, it is essential to use it judiciously and in moderation. Directly applying lemon juice or extracts to the skin should be done carefully and preferably diluted. It is recommended to consult with a dermatologist before incorporating *C. limon* into skincare routines, especially for individuals with sensitive skin or existing skin conditions (Behr *et al*., 2006; Hosseini *et al*., 2021; Madisha and McGaw, 2023).

Moreover, from the activities mentioned above, it has been determined that lemon exhibits several activities for protecting the human body from various pathophysiological alterations, thus providing an effective regimen in the natural drugs. The systematic diagram of the pharmacological activities of lemon is depicted in Figure 2.

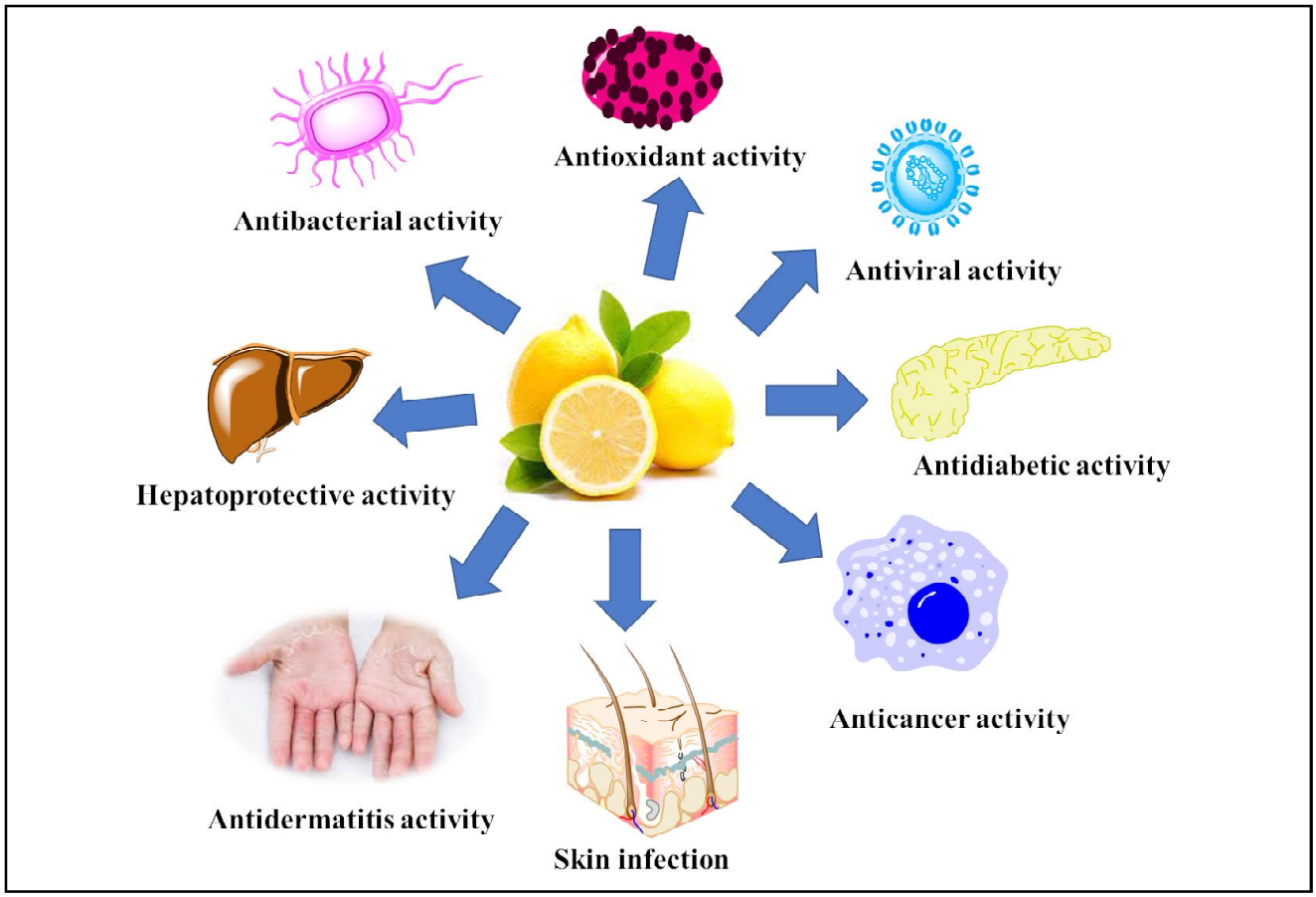

Figure 2: Systematic diagram of pharmacological activities *C. limon*.

6. The futuristic trend of *C. limon* in drug discovery and development

The speculate data on potential futuristic trends of *C. limon* in drug discovery and development is based on existing trends and possibilities as of that time. With the growing interest in natural products as sources of potential therapeutic agents, *C. limon* and its bioactive compounds may receive increased attention in drug discovery efforts. Researchers might explore the various phytochemicals present in lemon, such as limonoids, flavonoids, and essential oils, to identify novel drug candidates for multiple diseases (Caputo *et al*., 2020; Kim *et al*., 2014; Magalhães *et al*., 2023; Zhang *et al*., 2017). The ongoing research on lemon's potential antiviral properties may lead to identifying specific compounds that can inhibit viral replication or entry. Lemon-derived agents may be explored further for their efficacy against emerging viral infections, such as new strains of influenza or coronaviruses. Lemon's rich content of vitamin C and other bioactive compounds with immunomodulatory potential might inspire the development of drugs aimed at enhancing the immune response and supporting the body's defense mechanisms against infections and certain diseases. Lemon's skin-brightening, antimicrobial, and antioxidant properties could be utilized in developing dermatological products for skincare and treating skin conditions (Magalhães *et al*., 2023).

Formulations containing controlled concentrations of lemon extracts might be explored for their safety and efficacy in improving skin health. The antioxidant activity of lemon compounds might be investigated for potential therapeutic use in oxidative stress and inflammation conditions. Targeted antioxidant therapies may gain interest in areas like neurodegenerative diseases, cardiovascular health, and chronic inflammatory conditions. Given the complex nature of diseases, future research may explore combination therapies that include lemon-derived compounds and other drugs or treatments to enhance overall efficacy and reduce potential side effects. Advancements in nanotechnology could facilitate the development of innovative drug delivery systems using lemon-derived compounds. Nano-formulations might improve the bioavailability and targeted delivery of these compounds to specific tissues or cells (Aazza *et al*., 2014; Kim *et al*., 2014; Thilagamani *et al*., V, 2021; Woolley *et al*., 2012).

Furthermore, the demand for natural products as sources of potential therapeutic agents and exploration of compounds through advanced screening techniques and bioinformatics tools to identify promising drug candidates for various diseases is more likely to be grown for drug discovery and development. Researchers might intensify their efforts to discover new antiviral agents as the world faces viral threats, such as emerging infectious diseases and outbreaks. Lemon's reported antiviral properties might drive research toward isolating and characterizing specific lemon compounds that can effectively target viral infections. With a growing interest in immunotherapies and treatments that modulate the immune system, lemon's bioactive compounds may be studied for their potential immunomodulatory effects. Researchers might explore how these compounds can enhance immune responses against infections, allergies, or autoimmune diseases (Jain *et al*., 2012; Kim *et al*., 2014; Shaikh *et al*., 2022).

Lemon's potential benefits for the skin could inspire the development of novel dermatological products. Scientists might investigate how lemon compounds can be incorporated into topical formulations to address specific skin concerns, such as acne, hyperpigmentation, and aging. The concept of combination therapies, which involves using multiple drugs to target different aspects of a disease, may be extended to include lemon-derived compounds. Researchers might explore how combining lemon extracts with conventional medications or other natural products can lead to synergistic effects and improved treatment outcomes. Advancements in nanotechnology and drug delivery systems may play a crucial role in maximizing the therapeutic potential of lemon-derived compounds. Nanoparticle-based formulations enhance these compounds' stability, bioavailability, and targeted delivery to specific tissues or cells. As personalized medicine evolves, researchers might study the variations in individuals' responses to lemon-derived compounds. Genetic and metabolic factors could influence how patients metabolize and respond to these compounds, leading to personalized treatment approaches (González-Molina *et al*., 2010; Klimek-szczykutowicz *et al*., 2020; Murali *et al*., 2013).

However, the direction of *C. limon* role in drug discovery and development will depend on the continuous advancements in scientific research, technology, and medical practices. Researchers and pharmaceutical companies must conduct rigorous studies to validate the safety, efficacy, and potential side effects of any drug candidates derived from *C. limon* before they can be considered for clinical use.

Hence, it can be concluded that *C. limon* possesses a notable ethnopharmacological relevance as an adjuvant therapy. With a rich history of traditional use in various cultures, lemon has gained attention for its potential health benefits. Its bioactive compounds, including flavonoids, limonoids, and vitamin C, contribute to antioxidant, anti-inflammatory, and antimicrobial properties. These attributes align with its historical applications, such as aiding digestion, enhancing immune response, and promoting general well-being. As an adjuvant therapy, lemon's inclusion in complementary and alternative medicine practices has shown promise in supporting conventional treatments for conditions like colds, infections, and digestive disorders. However, rigorous scientific investigations are vital to validate and elucidate its mechanisms of action, interactions with medications, and optimal dosages. The ethnopharmacological significance of *C. limon* underscores its potential to enhance therapeutic outcomes and promote holistic health when integrated judiciously into diverse healthcare approaches.

7. Conclusion

In conclusion, *C. limon,* commonly known as lemon, possesses significant ethnopharmacological relevance as an adjuvant therapy. Its rich bioactive composition, including flavonoids, limonoids, coumarins, and phenolic compounds, contributes to its therapeutic potential across various health conditions. The traditional uses of *C. limon* in different medical systems highlight its historical significance as a therapeutic agent. Modern scientific research has provided insights into its molecular mechanisms of action, elucidating its antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anticancer, hepatoprotective, cardioprotective, neuroprotective, and dermatological activities. *C. limon* shows promise as a complementary or adjuvant therapy alongside conventional treatments. Its antioxidant and anti-inflammatory properties make it valuable in managing chronic diseases like cardiovascular disorders, neurodegenerative diseases, diabetes, and cancer. Additionally, its antimicrobial activity

and wound-healing properties benefit dermatological applications. However, further research, including clinical studies, is necessary to fully understand the optimal dosage, safety, and efficacy of *C. limon* based interventions. Integrating *C. limon* into evidence-based treatment strategies requires careful consideration and professional guidance. Nonetheless, the ethnopharmacological relevance of *C. limon* underscores its potential as a natural therapeutic resource, contributing to improved patient outcomes and promoting holistic healthcare approaches.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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