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Citrus Genus and its Pharmacological Activities: A Review

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ABSTRACT

Background: This review underscores the global distribution of citrus plants, diverse phytochemical composition, pharmacological properties and their uses.

Purpose: This paper reviewed the originating of Citrus genus from northeastern and central Australia, island Southeast Asia, near Oceania, and various subtropical and tropical regions in Asia. Paper elaborates the diverse phytochemical composition of citrus species contributes to their therapeutic characteristics. Citrus fruits, widely consumed and rich in nutrients and phytochemicals, have been linked through epidemiological studies to a reduced risk of several diseases.

Methods: The role of citrus plants according to their pharmacological activities explained in the paper with their possible mechanism of action.

Results: The citrus fruits contain phenolic acids, flavonoids, and coumarins ac chief chemical constituents. Pharmacologically, the citrus genus exhibits a spectrum of activities, including antioxidants, hypoglycaemic, antimicrobial, anticancer, antiulcer, anti-inflammatory, analgesic, anthelmintic, hepatoprotective, hypolipidemic, estrogenic, and neuroprotective effects.

Conclusions: Citrus plants have been shown in traditional and ethno medicinal literature to be especially beneficial in a variety of diseases.

1. Introduction

Mankind has always looked for treatments for different ailments and to relieve suffering. Up to 60,000 years ago, there is evidence that medical plants were used, but more recently, a five-thousand-year-old clay slab from Sumerian culture was found to confirm the usage of medicinal plants in medication manufacture (J.Summer, 2000). Despite the existence of advanced, ground-breaking technological advancements and contemporary medicine, traditional methods continue to be of utmost importance for the treatment of many ailments everywhere, including India. There are several reasons why the number of individuals utilizing traditional medicines is steadily rising. Traditional medicinal systems like Ayurveda, Homoeopathy, etc., are growing increasingly popular and fascinating around the world because of their approaches for both preventative and curative treatments. These medicines are easily available and have less toxicity and side effects compared to modern medicinal system. Components found in the environment naturally are used in traditional procedures. The bulk of these substances have both medical and nutritional advantages. Research findings show that nutrition significantly affects both general health and the treatment of several chronic illnesses (Katcher, H. I., *et al.*, 2009; Van Horn, *et al.*, 2008). Different chemical substances, such as secondary metabolites, found in plants have been shown to have uses in a variety of sectors, including the pharmaceutical industry (Sarrafchi, A., at el., 2015; Rabiei, Z., & Rafieian-Kopaei, M. 2014; Dangl, J. L., & Jones, J. D. G. 2001; Yamane, H., *et al.*, 2010; Eslami, M., *et al.*, 2016).Citrus is the most widely produced fruit in the world, and as consumer demand rises, so does production (Mahato, N., *et al.*, 2018).

The traditional medical system also employs plant components from members of the genus to treat a variety of conditions, including skin irritation, coughing, muscular discomfort, diarrhoea, vomiting, tumours, high blood pressure, and abdominal pain (Rafiq, S., *et al.*, 2018; Rudra, S. G., *et al.*, 2015; Mabberley, D. J, 2004; Arias, B. A., & Ramon-Laca, L. 2005). Due to the phytochemicals present in the Citrus genus, extensive study has been conducted (Al-Snafi, A. E. 2016). According to study on the phytochemical composition of the genus' members, these compounds include coumarin, limonoid, flavonoid, terpenoid, and terpene. The citrus genus has a large variety of fruits with a high yield and extensive market availability. The essential

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oils in the genus's fruit allow for the cultivation of several fruit varieties. Among the many uses for the fruit in the food industry are citrus juices, liquors, jams, tinned fruits, and preserved citrus. In terms of trade volume, citrus juice leads all other fruit juices (Yu, Y., Xiao, G., *et al.*, 2015; Miranda, R. F., *et al.*, 2019; Yuasa, M., *et al.*, 2021). Citrus wine retains to a large extent the original flavour and functional components of citrus, including a variety of vitamins, polyphenols, pectins, carotenoids, and fatty acids. The biological benefits of the nutrients in citrus wine include lung moisturization, preventing ageing, nourishment, liver nourishment, and stress relief(Selli, S. 2007). Fruits and citrus peel are dried using a variety of techniques to increase their shelf life, and the convenience requirement is satisfied by free-flowing powders that can be mixed with water to produce beverages with palatable flavours (Berk, Z. 2016; Tiwari, B. K., O' Donnell, *et al.*, 2009).

Citrus species have been traced back to Malaysia and China (Moore, G. A. 2001). Citron trees have been discovered in archaeological digs circa 4000 BC in Iran (Duarte, A., *et al.*, 2016).In 300 BC, Alexander introduced these fruits to the Greek and Roman. It has been described as the "fruit of Iran" or "the fruit of the media" in Greek and Roman literature. This fruit, considered to have been brought to the Philistines by the Greeks, is portrayed on one side of a Jewish currency made in 135 BC. During the Roman Empire, this fruit was produced in many locations of the empire. Furthermore, throughout the Renaissance, citrus tree farming spread, particularly to the northern part of the Mediterranean (Scora, R. W. 1975; Nicolosi, E., *et al.*, 2000;Jannati, M., *et al.*, 2009;Wu, G. A., *et al.*, 2018).

2. Botanical Description

Citrus is a genus of plants in the Rutaceae family that produces pulpy fruits with thick skins. According to The Plant List, the genus Citrus has 520 scientific plant names of species rank, 33 of which are approved species names. Lemon plants have thorny branches and white flowers with violet edges; the acidic, juicy fruit is oval (developed like an egg), has a fragrant skin that becomes yellow when ripe, and has a pronounced protrusion or nipple on the blossom end (Arias, B. A., & Ramón-Laca, L. 2005). Most Citrus species have huge evergreen bushes or small trees that grow to be 5-16 m tall (Singh, A., *et al.*, 2003). Citrus trees are evergreen plants that yield fragrant, flavorful, and juicy fruits in a variety of shapes and sizes (from round to rectangular). They have a tough, sturdy, and brilliant green to yellow peel or rind called epicarp or flavedo that covers and protects the fruits from injury. Its glands produce the essential oils which provide the fruit its distinctive citrus scent. It is made up of a white, firm, and spongy mesocarp that, jointly with the epicarp, forms the fruit's pericarp or peel. The pulp is the interior portion, which is split into various parts or juice pockets by a dense radical film or endocarp. This section is high in soluble sugars, ascorbic acid, pectin, fibres, organic acids, and potassium salt, which give the fruit its distinctive citrine flavour (Okwu, D. 2008; Roger, G. 1999; Roger, G. 2002).

3. Nutritional Value

Citrus fruits are often utilised as meals ingredients due to their great nutritional content. Their protective effect might be attributed mostly to the antioxidant activity of the bioactive substances found in them. Vitamin C, beta-carotene, flavonoids, limonoids, folic acid, and dietary fibre are the bioactive components responsible. A diet heavy in citrus fruits may lower the possibility of degenerative illnesses (Silalahi, J. 2002).Clonorchissinensis, Citrus limonum, and Citrus aurantifolia fruits included phenols, flavonoids, reducing sugars, steroids, terpinedes, and tannins (Rauf, A., *et al.*, 2014; Nalini, A., &Chimmad, B. 2003).

4. Health Benefits of Citrus and its Constituent

Table 1: Health Benefits of Citrus.

Activity	Phytoconstituents	Mode of action
Anti-cancer	Coumarins, Limonoids and Flavonoids	Anti tumar activities
Anti-oxidant	Phenolic compounds and ascorbic acid	Suppress superoxide anion and hydroxyl
Anti-inflammatory	Flavonoids and coumarins	Suppress TNF-α, interlukin-1β, interlukin-6, iNOS, COX-2
Diabetes	Hesperidine, Naringin, Neohesperidin and Nobiletin	Impove insulin sensitivity, Increase glycogen conc. Lower hepatic gluconeogenesis
COVID-19	Vitamin C, Anthocyanins, Flavanones, Hesperidine, Naringin	Binds to SARS-CoV and Inhibit its replication
Cardioprotective activity	Flavonoid, Nobiletin, Tangeretin	Reduce triglyceride levels

Breithaupt, D. E., & Bamedi, A. 2001; Singh, J., *et al.*, 2014; Padilla-Camberos, E., *et al.*, 2014; Heiss, E., *et al.*, 2001; Grosso, G., *et al.*, 2013).

5. Pharmacological Activities

5.1. Anti-oxidant Activity

C. limon essential oil demonstrates antioxidant activity by inhibiting lipoperoxidation, providing substantial protection against oxidative stress in mice. Additionally, it proves beneficial in mitigating the risk of lifestyle-related skin illnesses by maintaining the balance of oxidative stress (Campêlo, L. M., *et al.*, 2011; Campêlo, L. M., *et al.*, 2011; Bertuzzi, G., *et al.*, 2013).

5.2. Hypoglycaemic Activity

C. maxima has been proven to have anti-diabetic properties (Kharjul, M., *et al.*, 2014; Abdul, M., *et al.*, 2014). Aurantium L. improved blood lipid profile and liver enzymes considerably (Osfor, M., *et al.*, 2013). C. maxima significantly improved blood and lipid parameter (Sen, S., *et al.*, 2011; Oyedepo, A., &Babarinde, S. 2013). C. reticulate essential oil showed significant hypoglycemic action (Kangralkar, V., *et al.*, 2000). C. sinensis effectively lowered fasting blood glucose levels. The compounds hesperidin and naringin, found in C. sinensis, were specifically associated with significant reductions in blood glucose levels (Muhammad, N., *et al.*, 2013). In rats, diosmin decreased hyperglycemia caused by alloxan (Pradeep, M., *et al.*, 2007).

5.3. Antimicrobial Activity

Clinical isolates of Escherichia coli and other were all suppressed by C. Limon (Madhuri, S., *et al.*, 2014). C. sinensis has significant antibacterial activity, but C. aurantium has greater antifungal activity against Colletotrichumcapsici (Nada, K., *et al.*, 2013). Fresh as well as dried citrus and sweet lemon were found to have antibacterial activity against six various bacterial species and yeast isolates (Yekeen, M., *et al.*, 2014). C. sinensis is a powerful antifungal agent against Lentinussajor-caju (Shinkafi, S., & Ndanusa, H. 2013). C. limon is very effective against the bacterial species Propionibacterium acnes responsible to cause Acne vulgaris (Dhiman, A., *et al.*, 2012). C. sinensis fruit peel extract inhibited number of bacteria and number of species of fungus to varying degrees (Guerra, F., *et al.*, 2013). It has been found that the essential oil of Citrus limon has a strong biological potential against resistant to multiple drugs Acinetobacterspp (Moon, S. H., *et al.*, 2013). On Helicobacter pylori strains, hesperetin and naringenin demonstrated the most potent antibacterial action (Zhang, Y., *et al.*, 2013). Bergamot extract's antibacterial activities have been demonstrated to be more efficient against Gram-negative bacteria. Other studies validated the antibacterial action of naringin and its derivatives against Gram-positive bacteria (Degirmenci, H., *et al.*, 2019). C. aurantium f has demonstrated excellent antioxidant activity as well as broad-spectrum antibacterial activity. In the samples studied, phenols and flavonoids were shown to exhibit antioxidant and antibacterial activities. As a result, this plant has the potential to be employed as an antibacterial agent in functional food and medicine (Huang, S. M., *et al.*, 2012). It was seen in various studies that citrus plants have impactful antibacterial and antifungal activities.

5.4. Anti-ulcer Activity

Stomach ulcers are induced by different methods in experimental study. In acetic acid-induced chronic stomach ulcers, lemon juice a moderate ulcer healing effect and enhanced the effects of pantoprazole and ranitidine. The juice has an antisecretory and antiulcer effect in pyloric ligated rats. Lemon juice at both dosages had a strong antiulcer effect in ethanol-induced, stress-induced, and indomethacin-induced stomach ulcers. In cysteamine-induced duodenal ulcers, lemon juice also decreased ulcer area. Lemon juice combined with ranitidine or pantoprazole improves its antiulcer efficacy (Bhavitavya, B., *et al.*, 2012). Citrus lemon L. essential oil and limonene significantly protected stomach mucosa in an ethanol-induced lesion model (Rozza, A., *et al.*, 2011).

5.5. Anti-inflammatory and Analgesic Activity

C. medica L. peel extract has been shown to be effective in reducing carrageenan-induced inflammatory discomfort in rats (Sood, S., *et al.*, 2009). Tanaka Citrus latifoliaLimonin was isolated, by suppressing proinflammatory mediators contained in the inflammatory exudate, essential oil demonstrated anti-migratory effect. Extract of C. limon L. fruit rind inhibited paw oedema significantly (Sivakumar, N., &Venkataraman, R. 2010). When contrasted with diclofenac and morphine, Citrus decumana extract reduced paw volume and discomfort significantly (SoodS, *et al.*, 2009). The analgesic activity of C. medica Linn. was observed utilising the tail immersion technique and the hot plate method (Negi S, Anand B, *et al.*, 2010).

5.6. Anticancer Activity

Citrus limetta fruit peel extract was tested, and it significantly reduced tumour volume, viable tumour cell count, tumour size, and improved haematological parameters, white blood cell count, and life duration. These findings suggest that it may have potential as a natural therapeutic agent for the treatment of tumours. Further research is needed to determine

the specific mechanisms by which the extract exerts its anti-tumour effects (Sen S, *et al.*, 2012). C. aurantifolia oil was used and it had inhibited human colon carcinoma cells by 78%. It has the ability to prevent colon cancer by inducing apoptosis (Patil J, *et al.*, 2009). In vitro study conducted, C. limon essential oil was used as test substance and it exhibits a cytotoxic impact on the cancer cell line which shown its cytotoxic potential (Jomaa S, *et al.*, 2012). In another study which include Extract of C. aurantifolia, exhibited cytoprotective activity against aflatoxin B1-induced liver damage. It drastically reduced nucleic acid levels and decreased DNA fragmentation, demonstrating a beneficial impact (Shanmugam P, *et al.*, 2013). Flavanones have been found in studies to limit tumour development and cell cycle arrest, triggering cancer cell apoptosis via death receptors and caspase-related mitochondrial pathways (Hwang SL, *et al.*, 2012). Previous studies validated hesperetin's anti-cancer benefits on a variety of cancer types, including breast and colon tumours (Aranganathan S, *et al.*, 2008). Essential oils are used for many purposes in daily life activity, after number of research conducted **o**f them, they are now recognised as anticarcinogenic agents. It was found in study on Citral has been used as a cancer chemo preventive drug against inflammation-related carcinogenesis (Mulder GJ & Ouwerkerk-Mahadevan S, 1997).

5.7. Anthelmintic Activity

Citrus plants extract were tried against some species of larva. They were determined to have the high percentage of death (97%), as well as the shortest fatal time in as larvicides (Beecher GR, 1999). C. aurantium was shown to have potential anthelmintic efficacy against Indian earthworms. Diluted and concentrated juice was tested it was found that concentrated shown better activity when compared to diluted (Bilal H, *et al.*, 2012). The leaves of C. medica have been reported to have the ability to paralyse and kill earthworms (Bidkar J, *et al.*, 2011). Secondary metabolites in C. aurantiumflavedo have insecticidal effect against adults of Bactroceraoleae (Gmelin)(Bairagi G, *et al.*, 2011).

5.8. Hepatoprotective Activity

Citrus microcarpa peel extract protected male Sprague-Dawley rats' livers from acetaminophen-induced liver injury. Enzyme levels of liver were found to be significantly lower compared to normal (Siskos EP, *et al.*, 2007). In another study it was found that the effects of a C. limon L. fruit extract on experimental liver damage caused by carbon tetrachloride restored aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total and direct bilirubin levels in rats that had been changed by carbon tetrachloride poisoning (Casimiro M, *et al.*, 2010).

5.9. Hypolipidemic Activity

In another study on rats, hypercholesterolemia was induced and effect of various citrus plant juices was evaluated. Burmese substantially enhanced amount of good cholesterol and reduced the amount of bad cholesterol levels. From this study it was concluded that consumption of these juices may improve the lipid profile in hyperlipidaemic condition. Long-term consumption of C. sinensis and C. limon juices confers significant protection against hypercholesterolemia insurgency (Bhavsar S, *et al.*, 2007).

5.10. Estrogenic Activity

Herbal remedies are of great interest and are thought to be less toxic and free from side effects than any synthetic treatments, despite the existence of known estrogenic prescription medications. Research was conducted on animal for total duration of 90 days. The sperm count was significantly reduced for two months, after the administration of extract and fractions of C. limonum seeds, it restored to normal after 3 months days (Trovato A, *et al.*, 1996). In rats, an extract of C. medica seeds produced estrogenic effects such as increased uterine weight and vaginal epithelial cell cornification. In immature female rats, the petroleum ether extract retained strong estrogenic activity (Kulkarni T, *et al.*, 2012; El-Alfy T, *et al.*, 2012). In another study conducted on pregnant rats it was found that, an extract of Citrus hystrix displayed postcoital anti-fertility action (Patil SJ, *et al.*, 2008). In another finding the anti-zygotic activity of extract of C. limonum was observed. Administration of extract resulted in a reversible anti-fertility impact (Rodents were used in the study's conduct) (Pawinee P, *et al.*, 1985). C. medica Linn. was employed as a traditional/folkloric medicine to treat infertility (Kulkarni TR, *et al.*, 2005).

5.11. Neuroprotective Activity

Neurological illnesses have significantly grown in importance and prevalence. Oxidative stress and neuro-inflammation plays an important role in the progression of neuro degenerative diseases (Maurya R, *et al.*, 2004). Parkinson's disease is the world's one of the most prevalent neurodegenerative illness. Hesperidin's antioxidant activity shown in a study protect against this disease (Malhi BS, Trivedi VP, *et al.*, 1972). In another research conducted on epilepsy hesperidin, which affects the NO-cyclic guanosine monophosphate (cGMP) pathway, may enhance the treatment of epileptic diseases through Evidence-Based Complementary and Alternative Medicine (V. Gaur, *et al.*, 2011). The primary essential oils of Citrus aurantium are limonene (97.83%) and mirsen (1.43%), which are present

in roughly a tenth of these concentrations and have the capacity to act against central nervous system depression (A. Kumar, *et al.*, 2013; S. Deterre, *et al.*, 2011; F. Guillon and M. Champ, *et al.*, 2000).

6. Pharmacological Activities

Table 1: Pharmacological Activity.

Pharmacological Activity	Mechanism of Action
Anti-oxidant Activity	C. limon essential oil inhibits lipoperoxidation, offering substantial protection against oxidative stress.
Hypoglycaemic Activity	C. maxima, C. aurantium L., C. reticulate, and C. sinensis reduce fasting blood glucose levels.
Antimicrobial Activity	C. limon, C. sinensis, and C. aurantium demonstrate significant antibacterial and antifungal activities.
Anti-ulcer Activity	Lemon juice and essential oils from Citrus species exhibit antiulcer effects in various experimental models.
Anti-inflammatory and Analgesic Activity	Extracts from C. medica L., Citrus decumana, and Tanaka Citrus latifolia demonstrate anti-inflammatory and analgesic effects.
Anticancer Activity	Citrus limetta fruit peel extract, C. aurantifolia oil, and C. limon essential oil show anticancer properties.
Anthelmintic Activity	Citrus plants, including C. aurantium, exhibit anthelmintic efficacy.
Hepatoprotective Activity	Citrus microcarpa peel extract and C. limon L. fruit extract demonstrate hepatoprotective effects.
Hypolipidemic Activity	Consumption of citrus plant juices, including C. sinensis and C. limon, improves lipid profiles in hyperlipidaemic conditions.
Estrogenic Activity	Extracts from C. limonum seeds, C. medica seeds, and Citrus hystrix exhibit estrogenic effects.
Neuroprotective Activity	Citrus species, such as C. aurantium and C. limon, demonstrate neuroprotective effects. Hesperidin shows potential in Parkinson's disease and epilepsy.

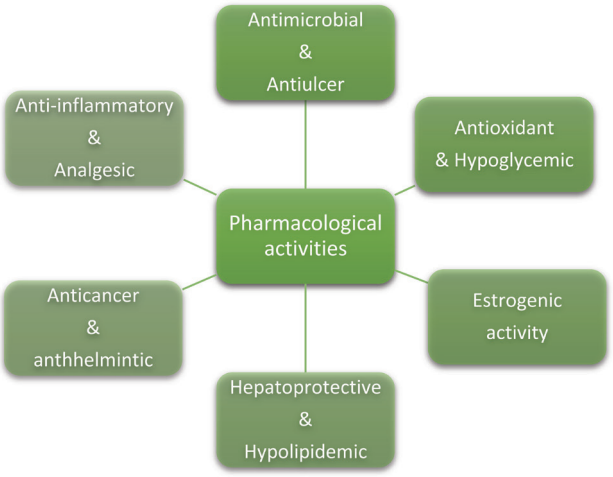

Figure 1. Pharmacological activities of citrus genus.

Conclusion

Citrus plants have been shown in traditional and ethno medicinal literature to be especially beneficial in a variety of diseases. They are widely available and have been shown to be effective in the treatment of a variety of illnesses. Antiulcer, analgesic, anti-inflammatory, neuroprotective, antioxidant, anthelmintic, hepatoprotective, antibacterial, and hypoglycaemic actions have been discovered in the plant. This article presents a comprehensive literature review on the health benefits of citrus, describing a variety of pharmacological activity of distinct citrus plant sections. Citrus plants might thus be classified as vital plants since they contain components that have been proved to have effective against health problems.

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All authors contribute equally inconceived and designed the paper, collection of data, and contribution in analysis, wrote paper and finalize it for publication.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Declaration

It is an original data and has neither been sent elsewhere nor published anywhere.

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