A comprehensive review on *Citrus macroptera* Mont.

Arunima Dhar, Esha Bala, Bimal K Chetri, Siddhartha Singha

Correspondence

Arunima Dhar[1], Esha Bala[1,2], Bimal K Chetri[1,3], Siddhartha Singha[1*]

[1]School of Agro and Rural Technology, Indian Institute of Technology Guwahati, Guwahati, Assam, 781 039, India
[2]Department of Engineering Sciences (Biotechnology), School of Engg. & Technology (SOET), Sandip University Nashik-422213, Maharashtra, India
[3]Department of Environment and Life Sciences, Sherubtse College, RoyalUniversity of Bhutan, Kanglung-42002, Trashigang, Bhutan

*Corresponding Author: siddharthafp@iitg.ac.in

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Review

Abstract

Background: Citrus macroptera, a member of the *Citrus* genus, holds significant potential for therapeutic applications due to its diverse pharmacological properties and biological activities. This review delves into the plant's taxonomy, morphology, and traditional uses, highlighting its role in various medicinal and culinary practices. The study focuses on the three main parts of the plant - fruit, leaves, and stem - and explores their wide range of pharmacological properties. These include antioxidant, cytotoxic, antimicrobial, thrombolytic, hypoglycemic, anxiolytic, anti-depressant, cardioprotective, and hepatoprotective activities which are proven in clinical studies.

Methods: A systematic search was done from relevant databases with keywords related to the study.

Result: The presence of phenolic acids, flavonoids, and tannins, acting synergistically as antioxidants, contributes significantly to these properties. The benefits of various plant parts extracts are also examined in the review. Notably, the fruit peel extract causes premature death to non-small cell lung cancer cells through prooxidant-induced apoptosis. Animal studies indicate that the fruit possesses an antioxidant capacity against acetaminophen-induced hepatonephrotoxicity as well as moderate α-amylase inhibitory activity and hypoglycemic effects in normal and glucose induced hyperglycaemic rats respectively.

Conclusion: C. *macroptera* could be a potential oral hypoglycemic agent source *in vitro*. This detailed review explores *C. macroptera* belonging to the Citrus genus, which has a wide range of pharmacological properties and diverse biological activities and hence may have significant therapeutic potential. The taxonomic classification, morphology, and traditional uses of this plant over time in various medicinal and culinary practices will be discussed.

Keywords: *Citrus macroptera*, Phytochemicals, Antioxidants, Antimicrobial agents, Traditional medicine, Therapeutic uses

Background

Plants have always been remedies since time immemorial, drawing upon such knowledge that has been accumulated and folk traditions. Their usage ranges over the disease continuum from acute conditions to chronic illnesses. Over the years, recent global research endeavors have led to a large body of scientific evidence highlighting the vast therapeutic potential of medicinal plants among many medical systems worldwide. *C. macroptera* is one promising citrus species with unique features and unparalleled potential. The plant has numerous active phytochemical constituents like limonene, *β*-caryophyllene, *β*-pinene, etc., which account for its pharmacological activities (Lalruatsangi *et al*. 2021).

In addition, studies have shown that *C. macroptera's* fruits, leaves, and stems have significant pharmacological properties, including antioxidant, cytotoxic, antimicrobial, thrombolytic, hypoglycemic, anxiolytic, anti-depressant, cardioprotective, and hepatoprotective. The plant is known for some actions; it inhibits *α*-amylase in vitro study; mitigates paracetamol-induced hepatotoxicity; and potentiates brain antioxidant enzyme activity (Alam *et al*. 2018, Hasan *et al*. 2021, Paul *et al*. 2017, Uddin *et al*. 2014). To enlarge the citrus biodiversity, enhance economic growth, and maybe support emerging industries, we can explore *C. macroptera* more widely (Hazarika *et al*. 2017). However, additional research is needed to fully reveal why it could be used for health purposes. Despite the numerous studies conducted over the years to ascertain biologically active compounds and their modes of action, there is a lack of definitive conclusions. Even though various theories have been proposed regarding how this plant works, more scientific data is required to validate its growing application. An extensive study should be carried out on the therapeutic potential of *C. macroptera*, which has high efficacy and versatility. This review comprehensively explores *C. macroptera*, focusing on its therapeutic applications, pharmacology, mechanisms of action derived from preclinical and clinical studies, safety considerations, and ongoing research potential. The aim is to guide future research towards achieving definitive outcomes for specific diseases.

Materials and Methods

Systematic search of databases was carried out using keywords relating to *Citrus macroptera*, its medicinal and nutritional values, and bioactive compounds within various scientific databases such as PubMed, Scopus, science direct, web of science and Google Scholar. Literature data gathered were collated under thematic categories: botanical characteristics, phytochemical composition, and pharmacological activities, drawing from their traditional uses Key words and commands used for Google scholar - "*Citrus macroptera*" and traditional uses of pharmaceutical or nutraceutical or conservation, PubMed- "*Citrus macroptera*" AND ("traditional uses" OR pharmaceutical OR nutraceutical OR clinical study OR morphology OR Conservation), Science Direct "*Citrus macroptera*" AND ("traditional uses" OR pharmaceutical OR nutraceutical OR clinical study OR morphology OR Conservation), Web of Science "*Citrus macroptera*" AND (traditional uses OR pharmaceutical OR nutraceutical OR clinical trial OR clinical study OR morphology OR conservation OR cultivation OR availability), Scorpus "*Citrus macroptera*" AND ("traditional uses" OR pharmaceutical OR nutraceutical OR clinical study OR morphology OR Conservation. The number of articles found was mentioned in Fig. 1. Studies focused on C. macroptera, its ethnobotanical uses, pharmacological activities, and conservation techniques were included in the study. All the research article included was in English language and original research.

Results

Botanical description and morphology

The genus *Citrus* belongs to the Rutaceae family (Webber1967). The **mandarin** (*Citrus reticulata* Blanco), **sweet orange** (*Citrus sinensis* (L.) Osbeck), **grapefruit** (*Citrus paradisi* Macf.), **lemon** (*Citrus limon* (L.) Burm. f.*),* and **lime** (*Citrus aurantifolia* (Christm.) Swingle) are among the most commercially significant fruits in the genus. *C. macroptera* is heterotypic synonym of *Citrus hystrix* DC*. C macroptera* is a commercially less known variety of *Citrus* genus that belongs to the Aurantieae tribe of the Aurantiodeae subfamily. Due to abundant citrus genetic resources, cultivated and wild, India is uniquely positioned in the "*Citrus* belt of the world" (Malik *et al*. 2013).

C. macroptera was first described by Father Montague on the Island of Art, which is located a few miles northwest of New Caledonia's northernmost point (Swingle 1943). This species is assumed to be native to Southeast Asia because it can be found in Thailand, Indo-China, Philippines, New Guinea, New Caledonia, Polynesia, and some other places (Bhattacharya & Dutta 1956, Khumukcham *et al*. 2017). This plant has also been reported to be cultivated in the semi-wild regions of India and Bangladesh. The citrus cultivation area covers 40% of the total in Mizoram, India, including *C. macroptera*, mandarin orange, lime/ lemon, and sweet orange. These areas have lower elevations and milder agroclimatic conditions, ideal for the species' development and yield performance (Hazarika *et al*. 2017).

Numerous studies have revealed the influence of topography and environmental factors on the characteristics of trees and their fruits. *C. macroptera*, commonly known as "**Hatkora**," is a small tree distinguished by its dense, rounded crown and smooth, thin bark (Fig. 3A)**.** The leaves of *C. macroptera* are evergreen, arranged alternately, and compound, consisting of 3-5 narrowly elliptic leaflets (Fig. 3B). Its flowers are white and fragrant, with five petals and numerous stamens. Sangma & Perinba documented variations in the size of **Hatkora** tree fruits and other parts. They found significant differences in plant height, ranging from 8 to 15 meters (Sangma & Perinba 2022). The leaves were dark green, had long petioles, and were orbicular. The fruit was spheroid with a concave base and a yellowish, rough surface (Fig. 3C). Fruit weight ranged from 440.67 g to 196.67 g, with an average of 603 fruits per tree annually. Peel thickness varied between 15.50 cm and 10.26 cm, while the number of seeds per segment ranged from 1 to 3. Similar findings were reported by Hazarika *et al*. for *C. macroptera* varieties found in different parts of Mizoram, India (Hazarika *et al*. 2017). They observed a maximum fruit weight of 617 g and a low pulp-to-fruit ratio ranging from 1.50 to 3.24. These studies demonstrate significant morphological variations in **Hatkora** collected from various regions of northeast India. Such variations are often observed in populations of the same species, particularly when they are geographically isolated for extended periods (Neri *et al*. 2018).

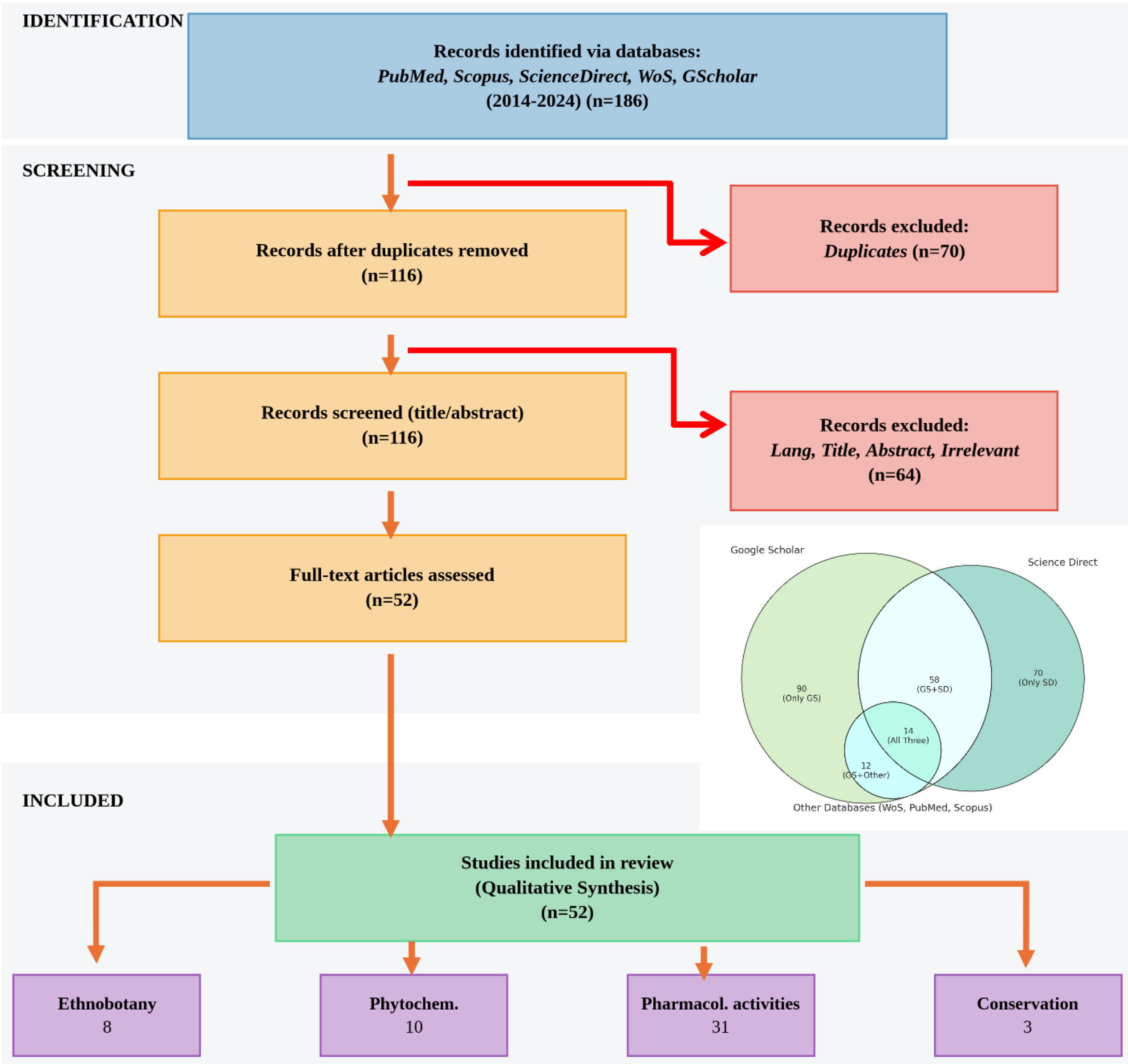

Figure 1. Prisma flowchart and distribution of articles from different databases with qualitative synthe**sis**

Ecological and cultural importance

C. macroptera in many regions, holds significant ecological and cultural importance, particularly in traditional medicine and culinary practices. Numerous studies have documented the traditional medicinal uses of *C. macroptera* in Ayurveda, folk medicine, and Chinese medicine (Aktar & Foyzun 2017, Hasan *et al*. 2019). It is traditionally used to treat food poisoning, fever, jaundice, and digestive and alimentary diseases. The plant's less explored compounds exhibit cytotoxic, antibacterial, antihypertensive, antipyretic, anti-diabetic properties, and stimulate appetite. This was confirmed by interviewing participants from different states in northeast India (Table 1).

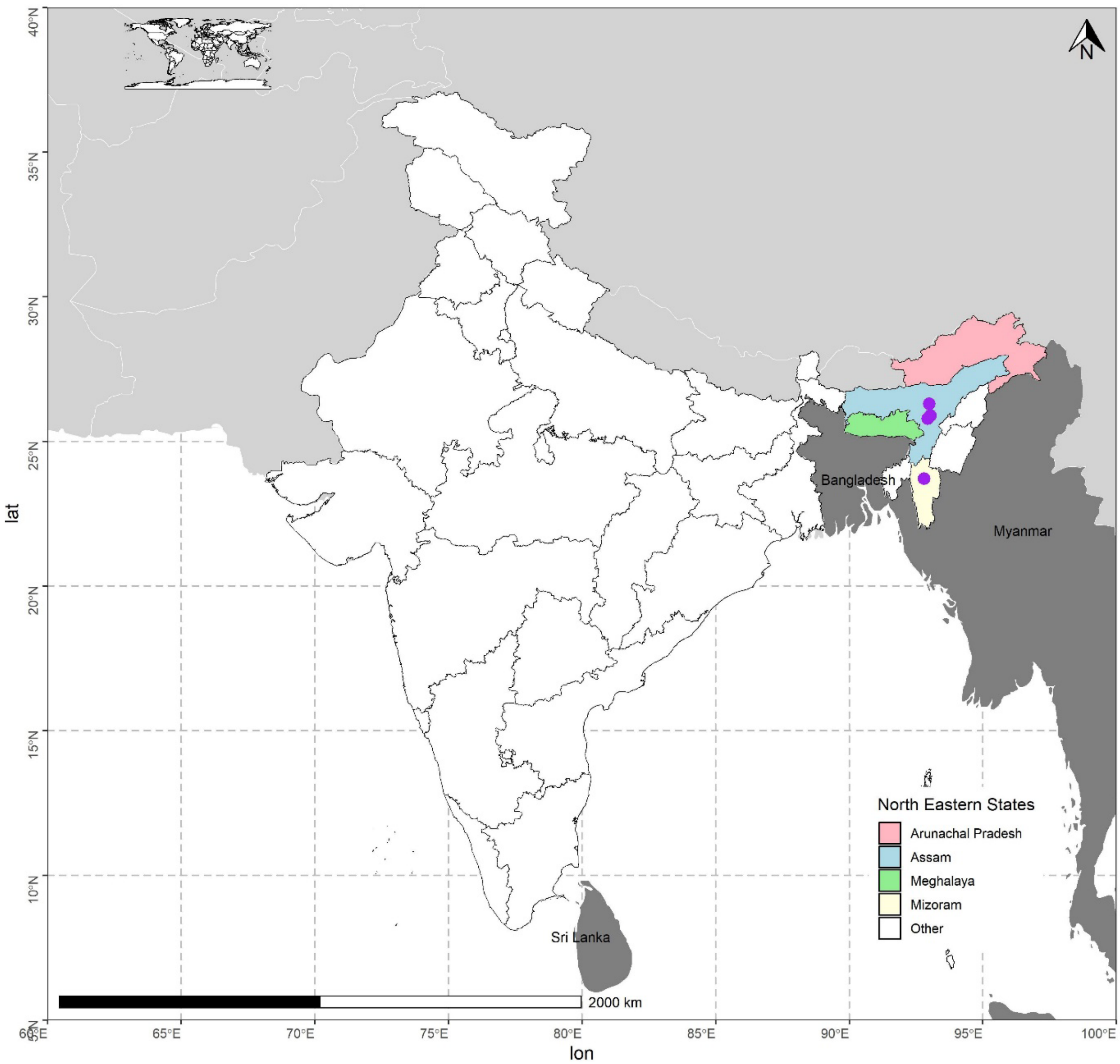

Figure 2. Native and introduced regions of *C. macroptera*, with distribution highlighted in the Northeastern states of India (Assam, Meghalaya, Arunachal Pradesh, and Mizoram).

Table 1. Traditional folk medicinal uses of *C. macroptera*

Place	Part used	Application	Reference
Manipur	Fruit	Fruit juice is used for stomach ailment, kidney stone and diabetes	Malik & Chaudhury 2006, Singh et al. 2014
	Peel	Fruit peels are used for treatment of dyspepsia, epilepsy	
Assam	Fruit	For digestion, rheumatic pains, colic.	Baishya *et al.* 2015
	Peel	Anxiety and depression	Rahman et al. 2014
New Caledonia	Whole fruit	Remedies against ringworm, complex remedies against epilepsy-like symptoms, antiprotozoal and nematocidal activities	Desrivot *et al*. 2007
Bangladesh	Whole fruit	Used for treatment of fever also stimulates appetite	Rahmatullah *et al*. 2010, Ahmed *et al*. 2021

The unique flavor of *C. macroptera* has led to its widespread use in culinary practices. While the fruit is quite sour and unappealing, its peel is highly valued. It is used fresh or dried, incorporated into candies, and employed as a flavoring agent in cooking due to its citric taste (Table 2). The fruit pulp is also used to make squash. In Manipur, *C. macroptera* fruit juice is used for stomach ailments, while the fruit peel serves as a spice and is employed in cases of dyspepsia (Singh *et al*. 2014). Overall, *C. macroptera*'s cultural and ecological significance stems from its diverse applications, ranging from traditional medicine to flavor enhancement in cooking. Its versatility underscores its potential for broader use and further research.

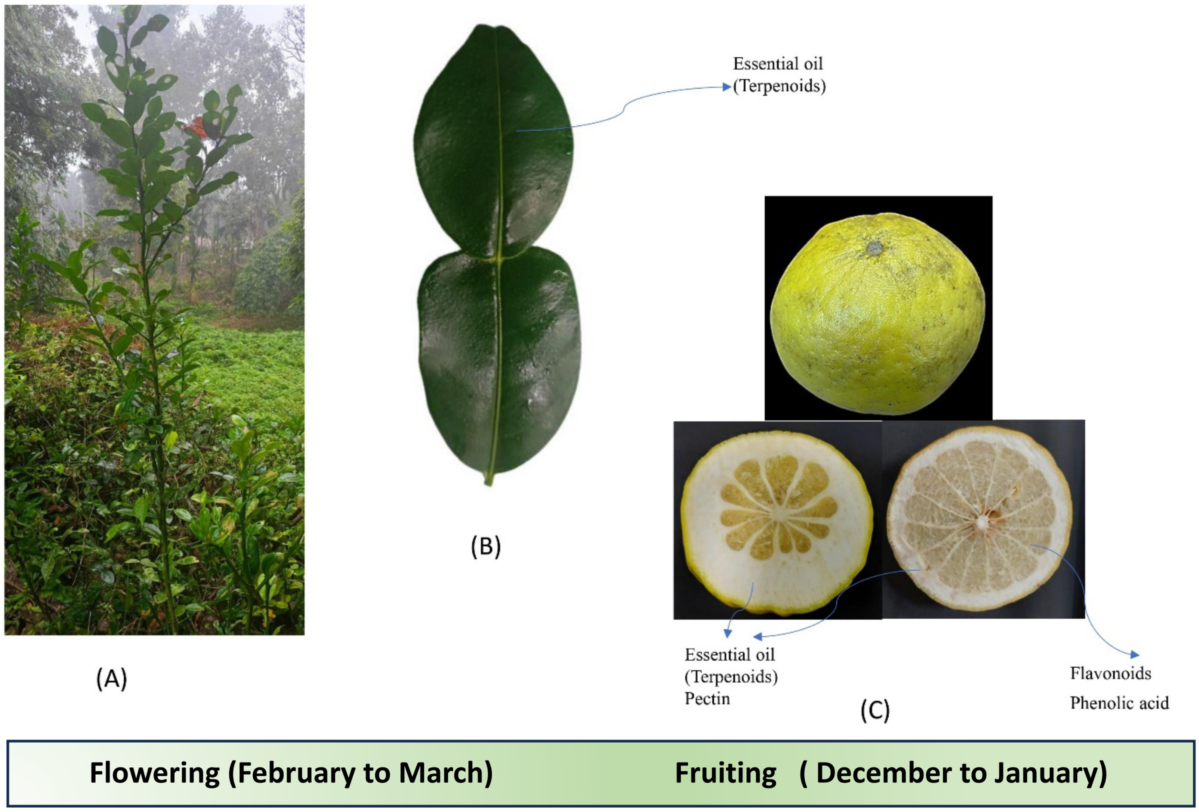

Figure 3. (A) *C. macroptera* tree (B) Leaf (C) Fruit

Table 2. Traditional culinary uses of *C. macroptera*.

Geographical area	Part of fruit used	Uses	Reference
Mizoram and Assam	Peel	Cooked With Lentil and fish in the form of decoction	De 2017
Meghalaya (Khasi Tribes)	Peel	Pork, beef, fish and chicken is cooked with fresh or dried fruit peel.	Upadhaya *et al*. 2016
	Pulp	Sundried and pickled	
	Juice	Used as a flavoring agent to cook pork. It is believed to neutralize fat.	
Meghalaya (Garo Tribes)	Peel	Fresh or dried peel is used to cook pork, beef, fish, and chicken. Delicacy Of *Garo* with This Fruit Is called As "*Wak Chambal Phura*" it is a pork preparation with peel.	Upadhaya *et al*. 2016
	Fruit	Sundried and pickled	
Manipur	Peel	Dried and used as spice element	Khumukcham *et al*. 2017
Bangladesh	Peel	The thick, fleshy rind of *C. macroptera* is eaten as a vegetable. The thick rind is cut into small pieces and cooked (either green or ripe) with beef, mutton, and fish curries. The peel is sun-dried and kept for future use.	Islam *et al*. 2015

Conservation challenges and propagation strategies for *C. macroptera*

C. macroptera faces significant conservation challenges, particularly in northeastern India, where it is classified as a wild endangered species (Malik *et al*. 2013b, Malik & Chaudhury 2006). Tissue culture techniques have emerged as an effective method for rapid multiplication and production of multiple shoots from apical parts of various citrus varieties (Hazarika *et al*. 2017). *In vitro* micropropagation techniques have also proven successful in producing secondary metabolites in large quantities, benefiting industrial and medicinal applications. Using callus cultures of nucellus tissue in *C. macroptera*, Miah *et al*. obtained significant results regarding somatic embryogenesis and plantlet regeneration. Within 7 days, a modified Murashige and Skoog medium supplemented with malt resulted in the development of some loose greenish calli. The plantlets were planted in the soil with a 100% survival rate (Miah *et al*. 2002). Further studies exploring 6-Benzyl Amino Purine (BAP) and Kinetin (Kn) applications for *ex vitro* rooting of shoots directly into the soil. The method achieved an average survival rate of 85-90% (Miah *et al*. 2008). Plant growth-related processes, such as an increase in plant height, root length, stem diameter, and leaf number, are all enhanced by Kinetin (Kn), which is important in plant growth and development. In addition, it promotes photosynthetic pigment formation besides enhancing photosynthesis and gas exchange rates among other physiological processes occurring within the plants' systems (Mielcarek & Isalan 2021). Also, kinetin application up-regulates the antioxidant system, thereby improving the activities of antioxidant enzymes and non-enzymatic components that help scavenge ROS produced during stress conditions (Othman *et al*. 2022). Besides, 6-Benzyl Amino Purine (BAP) is also another known plant regulator found in many plants. This technique is recognized as cost-effective and more efficient (Fig. 4). Additionally, older shoots showed better success in *ex vitro* rooting compared to younger ones, according to this research study.

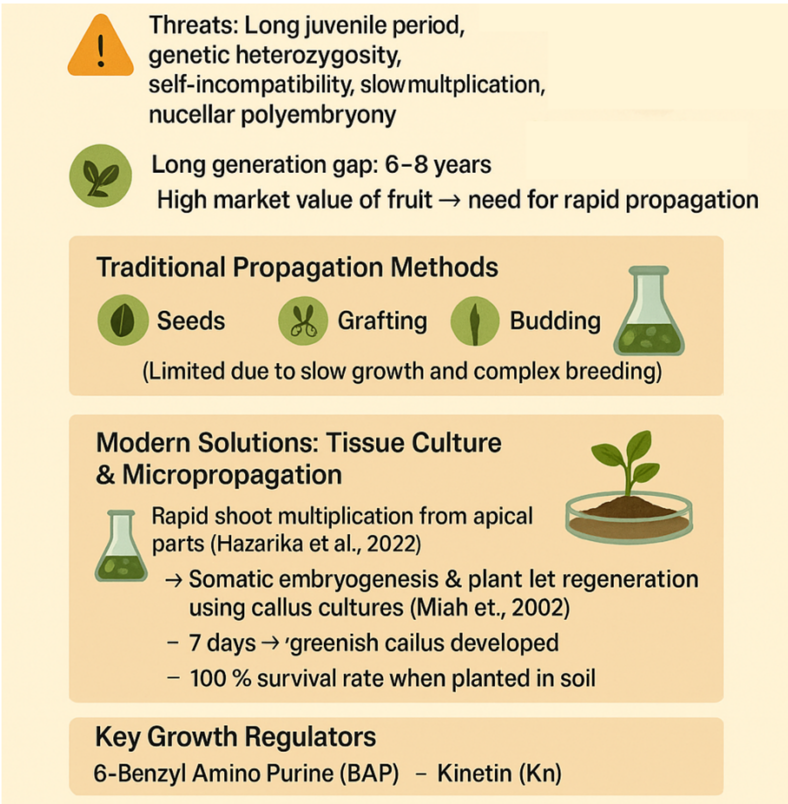

Figure 4. Conservation and propagation practices and research enhancement

Storage studies

C. macroptera is a seasonal and perishable fruit, necessitating research on storage techniques to maintain quality and stability over time. Islam *et al*. conducted storage studies at 5°C for 15 days and -18°C for 3 months (Islam *et al*. 2015). While antioxidant activity remained stable during storage, vitamin C content significantly declined. Initial vitamin C content was 210.43±0.40 mg/100g, decreasing during storage although the specific degree of decrease was not reported. Roy *et al*. explored drying kinetics and biochemical properties, finding that 45°C drying resulted in the highest retention of color, flavonoids, phenolics, vitamin C, citric acid, and B vitamins (Roy *et al*. 2022). Further research is needed to investigate changes in other nutrients, such as *β*-carotene and mineral composition. Also, there are no studies available in public domain about the effect of different environmental factors during the storage and transport of the fruit. Since the consumption is local and not as fresh fruits, the trade of the fruit is restricted to a few traditionally processed forms only, like sun-drying the peel and pickling the fruit (Table 2). Given the seasonal nature of *C. macroptera*, preservation, and processing studies are crucial to increase self-life and ensure year-round availability.

Functional properties

Semi-wild citrus species, *C. macroptera*, with its preclinical and clinical studies, have a number of functional properties. It is a fruit that contains important nutrients and demonstrates strong antioxidant activity (Islam *et al*. 2015). The essential oils obtained from fresh peels include limonene, beta-caryophyllene and geranial which contribute to the chemical composition (Uddin *et al*. 2014). Lupeol and stigmasterol, which are found in the stem of *C. macroptera*, have been associated with potential health benefits such as protection against oxidative stress, fibrosis, and liver damage (Alam *et al*. 2018). Singh *et al*. recognized 57 essential oils in the peel and leaves, out of which there were 10 identical compounds between the two parts of this tree (Singh *et al*. 2014). Table 3 shows major compounds with their relative percentages. Monoterpene hydrocarbons, limonene, oxygenated monoterpenes; sesquiterpene hydrocarbons; oxygenated sesquiterpenes comprise the peel of *C. macroptera* (Rana & Blazquez 2012), while Fig. 5 presents the primary compound groups and their structures. Hence, these outcomes reflect that *C. Macroptera* has varied chemical compositions implying potential functional characteristics as well as therapeutic applications for cure various diseases due to its medicinal values.

Table 3. Essential oil and phenolics present in *C. macroptera.*

Group of compounds	Part of fruits	Extraction method	Metabolites	Content	Reference
Essential oils	Peel	Grated peel were administered to hydro distillation for 3-4 hours and dried over anhydrous sodium sulfate	Bicyclo [4.1.0] heptane 7-(1-methylethylidene)	60.0%	Khumukcham *et al*. 2017
			7-(1-methylethylidene)	4.0%	
			Limonene oxide	3.5%	
			Trans Carveol	2.7%	
	Peel	Hydro distillation for 3 hours followed by extraction with diethyl ether	Monoterpene hydrocarbons	57.4%	Rana & Blazquez 2012
			Limonene	55.3%	
			Oxygenated monoterpenes	15.6%	
			Sesquiterpene hydrocarbons	12.7%	
	Leaf	hydro distillation for 3 hours	2-methylaminobenzoic acid methyl ester	57.2%	Khumukcham *et al*. 2017
			bicyclo [4.1.0] heptane 7-(1-methylethylidene)	23.2%	
			β-pinene	8.8%	
			ocimene<(E)-BETA->DB5-519	3.3%	
	Leaf	hydro distillation	Benzo(a)*pyrene*	25.3%	Waikedre *et al*. 2010
			p-Cymene	17.6%	
			Sabinene	4.8%	
			β -Pinene	33.3%	
			Limonene	2.4%	
			(E)-b-Ocimene	6.7%	
			g-Terpinene	3.1%	

Polyphenolic compound (mg/100g of dry extract)	Fruit (Edible part)	Ethanolic extract	Caffeic acid	428.36 mg/100ml	Alam *et al*. 2018
			Syringic acid	81.91 mg/100ml	
			(âˆ’)-epicatechin	33.87 mg/100ml	
			vanillin	52.46 mg/100ml	
			Benzoic acid	47.84 mg/100ml	
			kaempferol	2.12 mg/100ml	

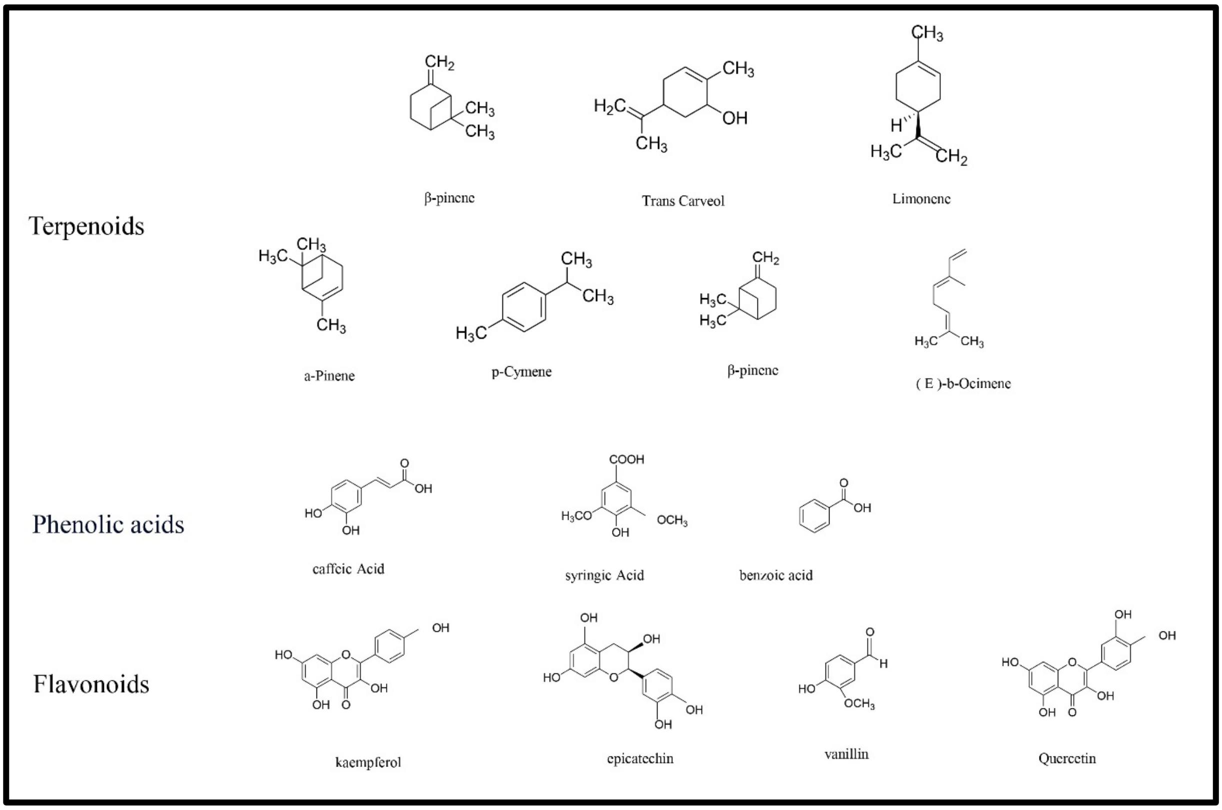

Figure 5. Major group of phytonutrients present in C. macroptera

Extraction of pectin from the peel using 95% ethanol yielded high pectin content. FTIR microspectroscopy confirmed the presence of ester, carboxylate ion, and carbohydrate groups in the extracted pectin. However, methoxyl (MeO) content was low (1.62±0.24%), indicating limited gel formation capacity (Islan & Rahman, 2017).

The fruit's proximate composition (Table 4) reveals a high vitamin C content, like other citrus varieties. While minerals like calcium, phosphorus, magnesium, iron, and sodium were identified, their concentrations were low. The high moisture percentage likely contributes to the increased activity of water-soluble enzymes and co-enzymes, which are crucial for metabolic processes. Vitamin C, *β*-carotene, thiamine, and riboflavin may contribute to the fruit's antioxidant properties. Compared to commercial citrus varieties like *C. limon*, *C. limetta*, and *C. aurantium*, *C. macroptera* exhibited the highest ascorbic acid content and a higher *β*-carotene content compared to *C. limon* and *C. limetta* but lower compared to *C. aurantium*. Further research is needed to confirm the specific contributions of these nutrients to the fruit's antioxidant activity. Mineral content was similar to other citrus varieties, except for a lower potassium content. However, *in vivo* and in vitro digestibility studies are necessary to determine the bioavailability and accessibility of nutrients.

Table 4. Comparison of common nutrients including microminerals of *C. macroptera* with other citrus fruits

Parameter	***C. macroptera* pulp (Islam *et al*. 2015)**	***C. limon* juice (IFCT 2017)**	***C. limetta* pulp (*IFCT* 2017)**	***C. aurantium p*\`ulp (*IFCT* 2017)**
Moisture (%)	90.40±2.0	91.59±0.53	91.32±0.33	89.61±0.19
Protein (%)	0.40±0.7	0.41±0.05	0.76±0.09	0.70±0.12
Vitamins (mg/100g)				
***β* Carotene**	22±1.50	2.62±0.34	2.54±0.30	31.94±2.12

Thiamine	0.08±0.01	0.04±0.007	0.06±0.005	0.07±0.009
Riboflavin	0.01±0	0.01±0.000	0.01±0.003	0.02±0.005
Ascorbic acid	210.43±0.40	48.16±4.35	46.96±7.64	42.72±4.81
Minerals (mg/100g)				
Calcium	25±1.0	0.009±0.006	0.001±0.00 1	19.52±1.48
Phosphorus	22±0.05	9.86±0. 5 2	20.55±1.27	12.90±4.47
Magnesium	10±0.75	8.90±0. 5 5	15.40±1.42	11.05±0.52
Iron	0.15±0.02	0.12 ± 0.0 5	0.72 ± 0.4 6	0.81±0.04
Sodium	3.5±0.01	1.21 ± 0.2 3	1.17 ± 0.4 5	1.47±0.05
Potassium	89±1.0	113±19.1	182±39.4	164±23.6
Copper	0.07±0.01	0.03 ± 0.0 1	0.03 ± 0.0 0	0.03±0.01
Zinc	0.21±0.01	0.08 ± 0.0 2	0.05 ± 0.0 1	0.04±0.01

Mechanisms of actions based on preclinical studies

To identify the specific bioactive compounds responsible for the observed health benefits of *C. macroptera*, preclinical studies are essential. Understanding the active principles of the fruit is crucial for developing targeted therapies, nutraceuticals, and novel drugs. This knowledge promotes natural alternatives with fewer side effects, enhances the economic value of the fruit, informs agricultural practices, and ultimately contributes to better public health outcomes by preventing chronic diseases. Preclinical studies typically utilize hydro-alcoholic extracts for optimal extraction, as demonstrated (Fig. 6). These studies provide valuable insights into the functions of bioactive compounds within *C. macroptera*. However, detailed toxicology and clinical studies are necessary to support this evidence-based knowledge and ensure safety and efficacy for dietary recommendations and drug development.

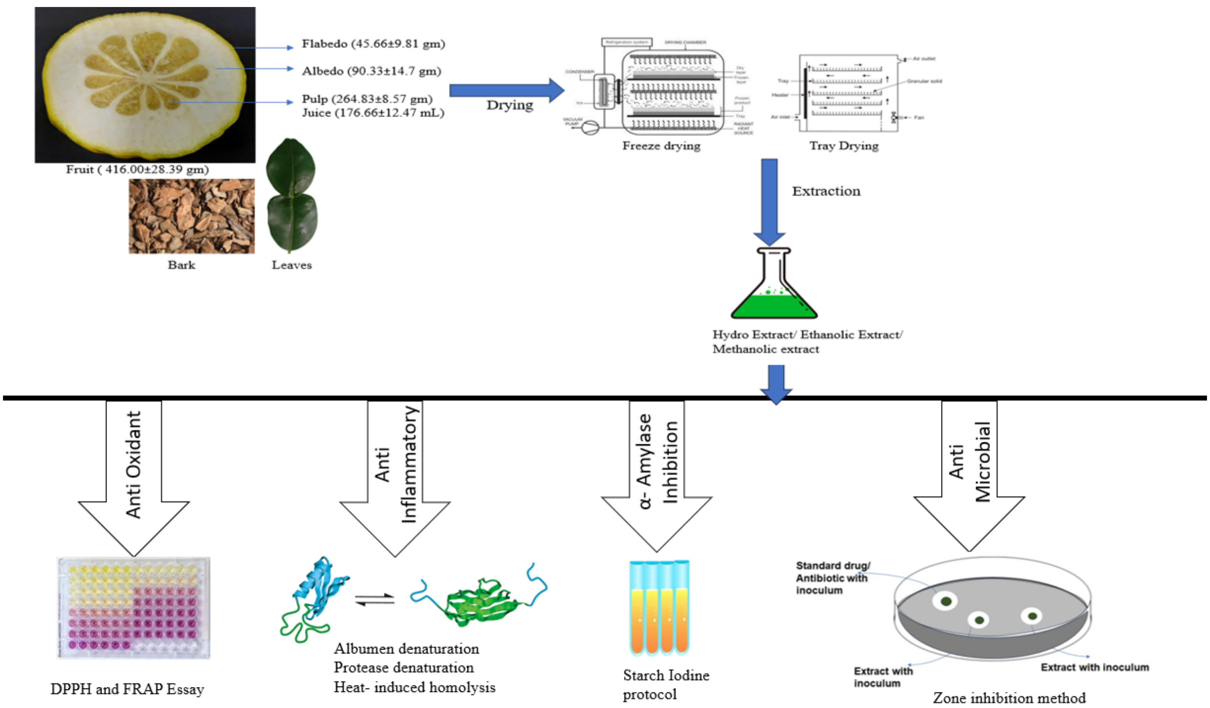

Figure 6. Assays for specific action of bio active compounds

Potential antioxidant capacity

Antioxidant activity has been demonstrated in *C. macroptera* research, with reference to the fruits' peels. The best antioxidant potential was observed in ethanol extract of *C. macroptera* fruit peels, similar to ascorbic acid (Rahman *et al*. 2014). Another proof is the presence of free radicals scavenging activity on the methanolic extracts from the hot maceration of the bark of *C. macroptera* (Chowdhury *et al*. 2008). Moreover, it is known that there are some biologically active substances available, such as limonene and beta-caryophyllene within a plant called *C. macroptera* (Lai *et al*. 2022, Talukder *et al*. 2023).

It should be mentioned that also essential oils have revealed antioxidant properties from the peel and leaf parts of *C. Macroptera.* DPPH radical scavenging activity and reducing power were used for the evaluation of anti-oxidant properties in vitro. Peel essential oil had a higher antioxidant capacity compared with leaf essential oil. The IC_{50} values for DPPH radical scavenging activity were determined at 118.07 µg/ml and 252.93 µg/ml for peel and leaf oils, respectively. The IC_{50} values for reducing power were found to be 122.5 µg/ml for the peel oil and 208.24 µg/ml for the leaf oil similarly. The peel oil also displayed a higher albumin denaturation assay, with an IC_{50} of 73.91 µg/ml compared to 87.48 µg/ml obtained from the leaf oil. The increased oil yield in the peel compared to the leaves suggests that the former is a more abundant source of volatile oil (Khumukcham *et al*. 2017).

In silico docking analysis revealed that proximadiol and menthone in citrus leaf extract had high binding affinities for NF-κB protein which plays roles in inflammation. Thus, *C. macroptera* leaf extract may be important to - citrus-related health products particularly for treating ROS-related ailments as well as tissue inflammations (Lala *et al*. 2023). A comparison study on freeze-dried and aqueous-dried extracts indicated that freeze-dried ones had better antioxidant capability (Sangtam & Thanzami 2020). In human non-small cell lung cancer cells, the use of *C. macroptera* has been shown to induce death, possibly by oxidative stress, thus signaling its potential as selective chemotherapeutic agent against this disease. It should be noted here that *C. macroptera* possesses multiple antioxidant phytochemicals such as significant flavonoids and phenolic acids.

Based on these findings, it can be concluded that high antioxidant capacity is found in the polar solvents *of C. macroptera* stem bark, especially its fruit peel. however, this assumption needs more careful examination into aqueous solutions. *in vitro*, antioxidant assays may not capture the in vivo antioxidant effect to substantiate the antioxidant activity of the fruit, multilevel, cell, and organism-based studies are to be performed. Research on the actual mechanism of its antioxidant activity remains limited. These findings suggest that *C. macroptera*'s enhanced antioxidant properties may offer protection against oxidative stress-related diseases and potentially contribute to overall human health. Nevertheless, in-depth studies on dose dependency and consumption mode are essential before promoting it as a health supplement.

Fig. 7 (A) highlights two potential avenues for mitigating oxidative damage: (1) direct reactivity with ROS/RNS as "free radical scavengers" and inhibition of oxidizing enzymes, leading to reduced cellular production of ROS/RNS; (2) chelation of transitional metals. The following oxidant enzymes contribute to ROS and RNS production: MPO (myeloperoxidase), LOX (lipoxygenase), XO (xanthine oxidase), COX (cyclooxygenase), NOX (NADPH oxidase), and NOS (nitric oxide synthase). Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), peroxiredoxin (Prx), thioredoxin (Trx), glutathione reductase (GR), and thioredoxin reductase (TR) play a crucial role in mitigating oxidative stress (Alaqeel 2024).

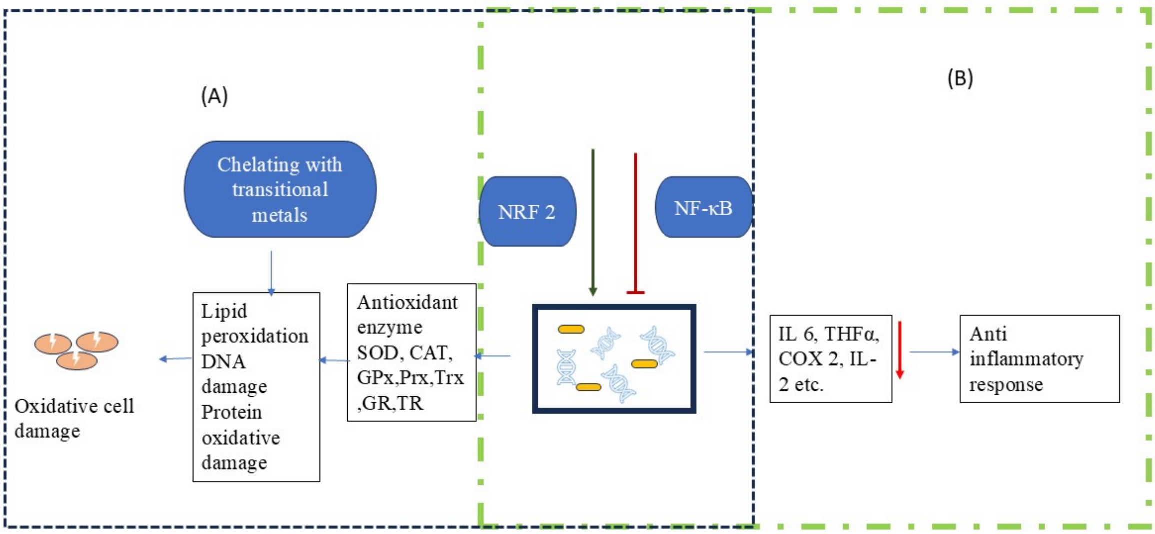

Figure 7. Mechanism of action of anti-oxidant (A) and anti-inflammatory (B) property (Tanigawa et al. 2007, Amitava & Kimberly 2014)

Potential anti-inflammatory effect

C. macroptera exhibits significant anti-inflammatory properties, likely attributed to the presence of terpene polyphenolic components or other active compounds (Bhutia, 2020). This aligns with the anti-inflammatory effects observed in flavonoids isolated from *Citrus aurantium* L., which have been shown to block the NF-κB and MAPK signaling pathways, ultimately deactivating pro-inflammatory cytokines like TNF-*α*, IL-6, and IL-2 while promoting the release of anti-inflammatory cytokines like IL-1 and IL-6 (Fig. 8 (B)). Similarly, crude methanol extracts of *C. aurantium* L. have demonstrated the ability to suppress proinflammatory mediators in macrophage cells via the NF-κB pathway (Kang *et al*. 2011). The anti-inflammatory effects of peel extracts from various citrus fruits, including *C. macroptera*, have also been documented. The peel oil inhibited protein denaturation and reduced heat-induced hemolysis, which was also more effective than leaf oil (Khumukcham *et al*. 2017).

These findings collectively suggest that *C. macroptera* possesses potent anti-inflammatory properties, making it a promising candidate for further exploration as a natural remedy with potential benefits in combating inflammatory conditions.

Potential alpha-amylase inhibitory activity

Alpha-amylase is an enzyme that serves to convert starch into maltose units. This enzyme inhibition is used for the treatment of metabolic disorders, including diabetes and obesity. However, such medications often cause disturbances such as diarrhoea, bloating and gas (de Sales *et al*. 2012). The bark of *C. macroptera* contains terpenoids namely lupeol known for *α*- amylase inhibition (Chowdhury *et al*. 2008). The inhibition is often dose-dependent and comparable to other commonly prescribed *α*-amylase inhibitors such as acarbose. Terpenoids such as oleanane, ursane, lupane, and saponins have been identified as potential anti-*α*-amylase agents. This was also evident in the animal studies where there was a drastic reduction of fasting blood glucose level at a 1000 mg/kg dosage (Uddin *et al*. 2014a).

Numerous flavonoids and citrus fruits have a high level of α-amylase inhibition, suggesting their potential utility in the treatment of diabetes and associated conditions. To clarify the impact of *C. macroptera* extracts on the α-amylase active site, more research is required. On contrary, it would be crucial to analyse the effects of active ingredients on the timing and composition of GI transit to demonstrate genuine routes and safety.

Potential antimicrobial capacity

Results have been obtained from research carried out on the antimicrobial effects of *C. macroptera*. When used to synthesize silver nanoparticles, fruit extract demonstrated strong anti-biofilm action against *B. subtilis* and *P. aeruginosa* (Majumdar *et al*. 2020) indicating its probable use as a natural antimicrobial agent. Various bacterial and fungal strains have shown antifungal properties in *C. macroptera* ethyl-acetate extracts of the fruit showed broad-spectrum antimicrobial activity against two gram-positive bacteria (*B. subtilis* and *Staphylococcus aureus*) and one gram-negative bacterium (*Escherichia coli*) (Uddin *et al*. 2014b). However, compared to the standard antibiotic azithromycin, its efficacy was lower.

Secondary metabolites extracted from the endophytic fungus *Talaromyces assiutensis*, found in *C. macroptera*, exhibited the highest antimicrobial activity against *S. epidermidis* (Lala *et al*. 2020). Endophytic fungi like *T. assiutensis* are known to produce various bioactive compounds with antioxidant and antimicrobial properties (Debbab *et al*. 2013; Rana *et al*. 2020). Table 6 compares the antimicrobial activity of *C. macroptera* with a standard drug. The essential oil extracted from the leaves of *C. macroptera* collected in New Caledonia exhibited pronounced activity against *T. mentagrophytes* var. *interdigitale* (Waikedr *etal*. 2010). *T. mentagrophytes* var. *mentagrophytes* is a dermatophyte fungus that can infect both humans and animals, causing various skin infections (Carter 1990, Varga 2014).

The plant extract can exhibit several mechanisms which promote the lowering the susceptibility of different microbial species. This could enter the cells by destroying cell membrane, causing DNA denaturation, DNA damage, inhibition of transcription and protein also inhibits the gene (Fig. 8) related to energy metabolism (Khameneh *et al*. 2021).

This finding underscores the potential of *C. macroptera* as a valuable antimicrobial agent for pharmaceutical applications. Being a potential inhibitor for opportunistic toxic bacteria like *aeruginosa or immune suppressor bacteria Staphylococcus aureus, along with dermatitis-causing bacteria, C. macroptera extracts exhibit a series of antioxidant activities*. The studies demand an in-depth analysis on the potential of inhibiting microbial growth and overall anti-microbial activity followed by dose dependency. These findings suggest that *C. macroptera* has potential antimicrobial properties that can be explored for pharmaceutical and agricultural applications.

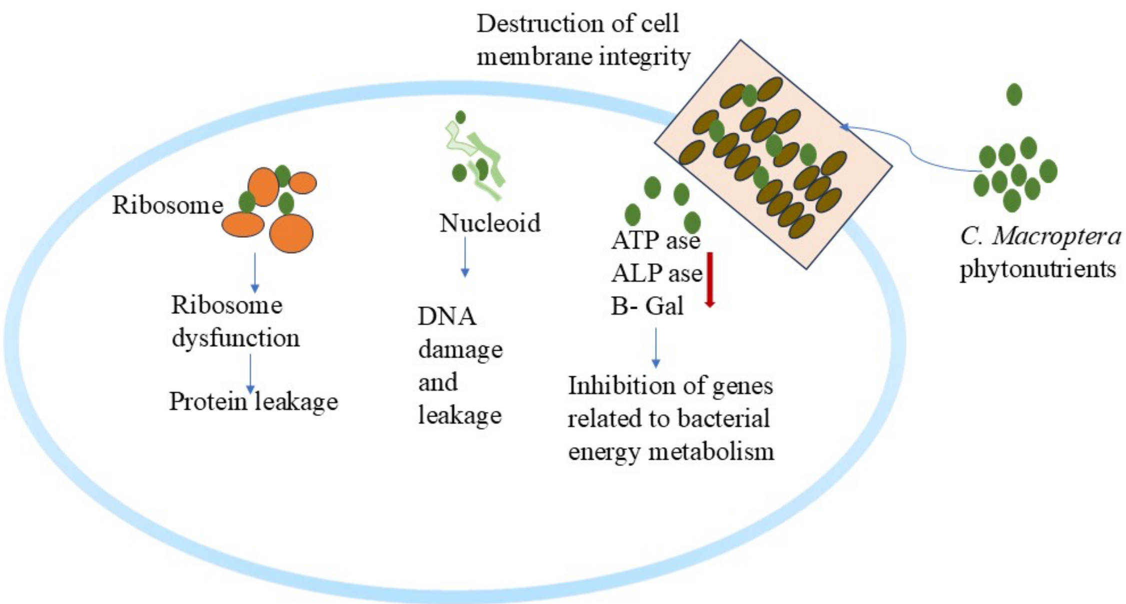

Figure 8 Mechanism of action of anti-microbial activity

Table 5. Anti-microbial activity of *C. macroptera* fruit pulp.

Treatment	***Anti-microbial activity***			**Reference**
	S. aureus	***B. subtilis***	***E. coli***	
Chloramphenicol (30 µg/disk)	25.5 ±0.707	NA	NA	Islam *et al*. 2016
Ethanolic extract (400 µg/disk)	13.5± 0.707			
% inhibition	47.06		--	
Azithromycin (30 µg/disk)	15.5±0.707	15.5±0.707	25.5±0.707	Uddin, *et al*. 2014b
Ethyl-acetate extract (400 µg/disk)	7.25±0.353	7.25±0.353	7.5±0.707	
% inhibition	75.45	53.23	75.45	
Methanol extract (400 µg/disk)	No inhibition	No inhibition	6.25±0.353	
% inhibition	--	--	70.59	

***In-vivo* animal level studies and specific pharmacological findings**

C. macroptera became the subject of extensive research due to its wide range contention in treating many diseases. From studies, the extract of *C. macropotera* has been proven to possess antioxidant, anti-inflammatory, and antimicrobial activity, thereby contributing to the functional roles in the prevention of cancer, diabetes management, and reduction of infections. Due to its possible relaxing and mood-boosting effects, there is much interest in using it as a functional ingredient for the treatment of depression and anxiety even extending to include hepatoprotective, cardioprotective, and neuroprotective activities (Khumukcham *et al*. 2017, Lala *et al*. 2023, Gogoi *et al*. 2021, Khameneh *et al*. 2021). This is also elaborated in more detail with confirmation based on clinical studies at the animal level (Table 6). Plant extract showed significant activity against enzymes involved in this debilitating neurological disease (Hossain & Biswas 2018, Alam *et al*. 2018). *C. macroptera* fruits have been reported to exhibit a hepatoprotective and nephroprotective effect in acetaminophen-induced liver damage (Paul *et al*. 2016). This immunity is credited to the plant and its abundance of polyphenols such as phenolic acids, flavonoids, tannins which quench free radicals and resist oxidative injury. Moreover, the peel extract showed more potent activity against isoproterenol-induced toxicity in rats (Uddin *et al*. 2014c) compared to pulp powder. The mechanism involves improving lipid metabolism, boosting natural antioxidant and anti-inflammatory. Compounds like vanillic acid, caffeic acid, syringic acid, and benzoic acid contribute to these protective effects.

These studies demonstrate the significant potential of *C. macroptera* in treating various diseases, from heart and liver issues to diabetes and Alzheimer's disease. Further research is needed to fully explore its therapeutic potential and to develop safe and effective treatments based on its remarkable properties. The diverse range of bioactive compounds found in *C. macroptera* contributes to its wide range of pharmacological effects. These include antimicrobial, antifungal, antiviral, antiallergic, antispasmodic, antihyperglycemic, anti-inflammatory, and immunomodulatory properties.

Table 6. *In-vivo* (animal level) clinical studies on various parts of *C. macroptera*

Specific function	Part of fruit used	Active component	Study animal	Control/ standard/ treatment used	Test Doses	Response	Remarks	Reference
Cardioprotective	Methanolic extract of dried fruit (Fruit: solvent 5:10)	Saponins, steroids and terpenoids	Sprague-Dawley female rats	Control-saline water	250 mg/kg, 500 mg/kg, 1000 mg/kg Body weight for 3 weeks	Elevated HDL (9%) and decrease in LDL (93%), TG (49%) Reduced HbA1c (30% for lowest dose) Lower liver enzymes like ALT (6%), AST (4%) at highest dose No inflammatory and necrotic features in the primary body organs	Significant reduction in HbA1c for lowest dose and A little reduction of liver enzyme level showed further research needed to establish the suitable dose. Change in lipid profile showed potential cardioprotective effect	(Uddin *et al*. 2014 c)
Cardioprotective	Ethanolic extract of air dried fruit and peel	saponins, steroids and terpenoids	Male albino Wistar rats	Control-saline water Treartment-Isopropanol (ISO)	500 mg/kg peel extract, 500 mg/kg pulp extract (methanolic) for 45 days	decreased cardiac enzymes reduced levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), while restoring high-density lipoprotein cholesterol (HDL-C) levels.	*C. macroptera* peel extract showed better protection against myocardial infarction in rats. Although peel extract with ISO diet was less efficient compared to peel extract along. It demands more study on dose determination. polyphenols from fruit extracts can bind with bile acids to increase their excretion, which may contribute to the lowering of cholesterol levels.	(Paul *et al*. 2017)
Hypoglycaemic	Methanolic extract of dried fruit	Polyphenols and saponins	Sprague-Dawley female rats	Control-saline water Standard-5mg/kg glibenclamide	500 mg/kg and 1000 mg/kg body weight	A dose of 1000 mg/kg and glibenclamide showed significance change in blood parameters. It showed 60% lower fasting blood glucose and similar trend in post prandial blood glucose.	*C. macroptera* fruit is safe for diabetes patients. Polyphenols and saponin present in fruit may be inhibiting this carbohydrate hydrolysing enzyme.	(Uddin *et al*. 2014a)

Neurological	Ethanolic extract of air-dried peel	Alkaloids, tannins, terpenoids, phenolic compounds, flavonoids, and volatile oils	Mice male and female	Control Olive oil Standard Imipramine; 10 bmg/kg and Phenytoin (25 mg/kg) and Phenytoin (25 mg/kg) in 1% tween 80	Peel extract 250 mg/kg and 500 mg/kg.	The Elevated Plus Maze (EPM) test showed a positive result Increased time spent in the light chamber in the Light and Dark Model (LDM) test Forced Swim Test (FST) and Tail Suspension Test (TST) decreased duration of immobility, no anti-epileptic activity seen. Increased level of brain antioxidant enzymes	Anxiolytic and anti-depressant effect seen However, the extract did not possess anti-epileptic properties. The primary citrus flavonoids may also cross the blood-brain barrier, and neurodegenerative disease intervention.	(Rahman *et al*. 2014)
Anti-cancer	Freeze dried juice	lectins, polyphenols, and flavonoids	Male Swiss albino mice	Control-saline water	25, 50, and 100 mg/kg/day dosage	Induced the expression of apoptosis regulatory genes, including caspase-8, caspase-9, cytochrome-c, and caspase-3, suggesting its potential anti-cancer activity.	*C. macroptera* fruit pulp juice demonstrated significant anti-proliferative activity both in vitro and in vivo, These findings support the traditional use of *C. macroptera* in folk medicine for its anti-cancer properties. Polyphenols inhibit oxidation, cleanse foreign substances, cause cell death, and boost immunity.	(Hasan *et al*. 2019)
Hepatorenal	Ethanolic extract of sun-dried fruit pulp	The bioactive compounds present in *C. macroptera* fruit are likely responsible for its antioxidant properties and protective effects against oxidative damage.	Male Wistar Albino rats	Control-saline water Standard-Silymarin Treatment-acetaminophen or *N*-acetyl-p-aminopheno	doses of 250, 500, and 1000 mg/kg for 30 days	Treatment lowered ALT and GGT levels decreased AST, ALP, and LDH activities decreased serum TB levels. decreased TC and TG levels. Reduced CRE, urea, UA, Na+, and K+ levels and increasing Cl- levels. It also reduced liver and kidney tissue lipid peroxidation levels.	These findings highlight the potential of *C. macroptera* as an inexpensive food product that can be consumed daily for prophylaxis against liver and kidney diseases caused by toxins.	(Paul *et al*. 2016)

Hepato protective	Dried peel powder	The presence of phenolic compounds, such as vanillic acid, caffeic acid and syringic acid and benzoic acid. and (-) epicatechin, in *C. macroptera* peel powder was identified through HPLC-DAD analysis	Evans female rats	Control- saline water Treatment- carbon tetrachloride	4 groups were studied 1 control group 2nd group olive oil and peel powder Group 3 was treated with CCl_4 in olive oil Group 4 received CCl_4 in olive oil, along with peel powder	reduced liver marker enzymes (ALT, AST, ALP) and oxidative stress parameters in CCl_4-treated rats. increased cellular antioxidant activities and glutathione levels. Decreased necrotic zones, fibrosis, and inflammatory cell infiltration reduced fibrosis and iron deposition in the liver. Decreased lipid peroxidation level in plasma and liver tissues	*C. macroptera* exerts hepatoprotective activity via promoting the antioxidant defines. Derivatives of caffeic acid prevents the liver damage and decreased the liver marker enzymes activities.	(Alam *et al*. 2018)

Toxicity studies

Before the clinical application of *C. macroptera*, its safety needs have to be established. Animal studies might give slight information regarding application; however, those studies aren't always accurately predictive of how humans may respond. Several studies have employed animal models to establish potential safe doses of *C. macroptera*, primarily about the pulp and leaves (Table 7).

Table 7. Toxicity studies of *Citrus macroptera*

Study	Extract Type	Animal Model	Dose	Findings	Reference
Acute toxicity study	Methanolic extract (pulp)	Rats	4 g/kg (single dose)	No toxicity observed	Uddin et al., 2014c
Sub-chronic toxicity study (30 days)	Ethanolic extract (pulp)	Male Wistar albino rats	1 g/kg/day	No adverse effects	Paul et al., 2016b
Leaf extract study	Leaf extract	Rats	2 g/kg	Safe dosing limit observed	Lala et al., 2020

C. macroptera appears to have a safe margin for dosing in both 4g/kg and 2g/kg dosing in animal studies, we need to be aware that human toxicity differs. Toxicologists define the safety margin as the estimate of the dose of a substance that produces adverse effects in the animal model relative to the human dose level (i.e., the human expected exposure). A wider safety margin is best unless the adverse effects become notable (Atkins *et al*. 2020). Based on animal studies, *C. macroptera* seems safe at a dose of less than or equal to 2000 mg/kg body weight. To establish the efficacy in human studies further evaluation of the safety and efficacy of *C. macroptera* needs to be done. This evaluation would establish dose-response in humans while ultimately providing clinical studies in trials to evaluate safe and effective doses of *C. macroptera*.

Synthesis: Bridging Traditional Knowledge and Scientific Evidence

Traditional knowledge of *C. macroptera*, a plant used in South and Southeast Asia for centuries, has been substantiated by scientific exploration. The plant contains a diverse range of bioactive compounds, including flavonoids, alkaloids, tannins, saponins, terpenoids, and essential oils, which are known for their antioxidant, antimicrobial, anti-inflammatory, analgesic, and hepatoprotective activities. These findings support traditional claims of its use against chronic inflammatory diseases and general health tonics. Antimicrobial studies have shown that essential oils and methanolic extracts from the fruit and peels can inhibit the growth of pathogenic bacteria and fungi, correlating strongly with its ethnomedicinal application in treating infections. However, challenges remain in bridging the gap between traditional knowledge and scientific validation. Most current studies are limited to in vitro assays or preclinical animal models, with a lack of extensive human clinical trials to confirm safety, efficacy, and dosage parameters.

Conclusion

C. macroptera is a natural reservoir of several biomolecules that exert activities from antioxidant, anticancer, anti-diabetic, and anti-microbial activities. This illustrates the scope of the discoveries of how the hidden potentials can be used for traditional uses and modern applications in ways to culture and consume this ample resource material effectively. Conducting research on sustainable cultivated practices and the post-harvesting process may lead to value-added products produced from *C. macroptera*. Aside from these issues, *C. macroptera* provides medicinal value and possibilities of unique aromatics involved in producing pharmaceuticals and cosmetics. More fundamentally, *C. macroptera* research can foster innovation in agriculture, industry, and medicine to broaden sustainable approaches toward biodiversity conservation. It is imperative that the fruit is included in fresh or processed form in the human diet. The present review should trigger more studies on postharvest handling of the fruit and other plant parts. Moreover, the anecdotal and pre-clinical evidence of its biological activities requires validation in its consumable form. In this respect, *C. macroptera* based products like juice, aqueous/hydroalcoholic extracts, peel powder, etc. should be carefully characterized and subsequently selected for pre-clinical and clinical studies.

Declarations

List of abbreviations: DPPH: 2,2-Diphenyl-1-Picrylhydrazyl; IC50: Half maximal inhibitory concentration; NF-κb: Nuclear Factor-kappa B; ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; MAPK: Mitogen-Activated Protein Kinase; TNF-α: Tumor Necrosis Factor alpha; IL-6: Interleukin-6; IL-2: Interleukin-2; DNA: Deoxyribonucleic Acid; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; TG: Triglycerides;, HBA1C: Hemoglobin A1C; ALT: Alanine Amino Transferase; AST:

Aspartate Amino Transferase; CGT: Carrier Genetic Test; ALP: Alkaline Phosphatase; CRE: Carbapenem-Resistant Enterobacterales; UA: Uric acid.

Ethics Approval: Not applicable

Consent for publication: All authors consent for publication

Availability of data and material: All data and material can be made transparent.

Declaration of competing interest: The authors declare that they have no competing interests.

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