REVIEW

Review of the nutritional composition, medicinal, phytochemical and pharmacological properties of *Citrus reticulata* Blanco (Rutaceae) [version 1; peer review: awaiting peer review]

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Abstract

Citrus reticulata Blanco is a moderately-sized fruit tree widely used as herbal medicine worldwide. The nutritional composition, medicinal uses, phytochemistry and pharmacological properties of *C. reticulata* were critically reviewed in the current study. The literature linked to *C. reticulata* properties was obtained from multiple internet sources including Elsevier, Google Scholar, SciFinder, Web of Science, Pubmed, BMC, Science Direct, and Scopus. Ethnopharmacological research identified antioxidants such as vitamin C, carotenoids and phenolic compounds, also a source of sugars, organic acids, amino acids, pectins, minerals and volatile organic compounds as components of *C. reticulata*. As a medicinal plant, *C. reticulata* is used for the treatment of dyspepsia, gastro-intestinal distension, cough with profuse phlegm, hiccup and vomiting. The crude extracts of *C. reticulata* fruits have depicted anti-inflammatory, anticholesterolemic, analgesic, antiasthmatic, antiscorbutic, antiseptic, antitussive, carminative, expectorant, stomachic. With more people becoming nutrition-conscious, there has been an increase in the demand for the use of citrus fruits and their by-products as traditional medicines for conventional healthcare in developing countries.

Keywords

Citrus reticulata, medicinal, nutrition, pharmacological, photochemistry

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Citrus reticulata Blanco is a large species belonging to the family Rutaceae, with various varieties and hybrids[1]. It includes popular citrus types such as Satsumas, Clementines, Tangerines[2] and the Mediterranean mandarin[3,4]. Tangerine is a group of orange-coloured citrus fruits consisting of mandarin hybrids[5], although the term tangerine is used interchangeably with mandarin.

Mandarins, like other citrus species, are indigenous to the subtropical and tropical zones of Asia, particularly China and Cochin-China[6,7]. Some researchers have reported that mandarins, alongside other citrus species, evolved in a region including Vietnam, South China, India and Japan[8,9]. They are now widely cultivated around the world in the warm temperate and tropical areas[8,10–12]. Mandarins account for 22–25 per cent of world citrus production among the commercially cultivated citrus species[9,13,14]. The major citrus growing regions of the world and their estimated output is shown in Figure 1.

Mandarins, including both monoembryonic and polyembryonic cultivars and many interspecific hybrids, are the most diversified category of citrus fruits[15,16]. Nevertheless, a remarkable similarity has been documented between mandarin cultivars at molecular and isoenzymatic levels[17–19]. There are 36 mandarin species, according to Tanaka[20], while Swingle recognized only three species, one of them being *C. reticulata* consisted of 34 species of Tanaka's system[21]. Chromosome studies have shown that the genus has a stable chromosome number of 2n=18, except for a few polyploids, with a small number of chromosome markers in the conventional karyotype[22]. The medicinal uses, phytochemistry and pharmacological properties of *C. reticulata* were examined in the current report.

Botanical description

The mandarin plant is a spiny, evergreen, bushy shrub growing 2-8 m tall[23] with most varieties averaging 7.5 m[13]. The tree has a dense top with slender branches bearing dark green, lance-shaped leaves with a prominent midrib. Petioles are narrowly winged or slightly margined. This tree bears white scented flowers followed by oval to flattened, sweet-fleshed, golden fruits[13]. The mandarin fruit resembles other oranges, is smaller and more oblate than oranges, round in shape, orange in colour, sweet in taste, with a thin, loose, easy-to-peel skin and can be easily damaged by cold. The fruit is up to 8 cm in diameter with easily separable segments[2].

Flowering is induced through low-temperature stress or soil water deficit stress[24,25]. Under subtropical climates, flowering is an annual event occurring during spring[26–28]. In tropical areas, flowering is a continuous event, mostly determined by moisture availability from sufficient rain or water supply[27–29] while in temperate regions it occurs with the onset of winter[30].

Methods and justification of the study

The literature search was performed from March 2020 to June 2020. A mixed-method review approach which involved combining quantitative and qualitative research was used to

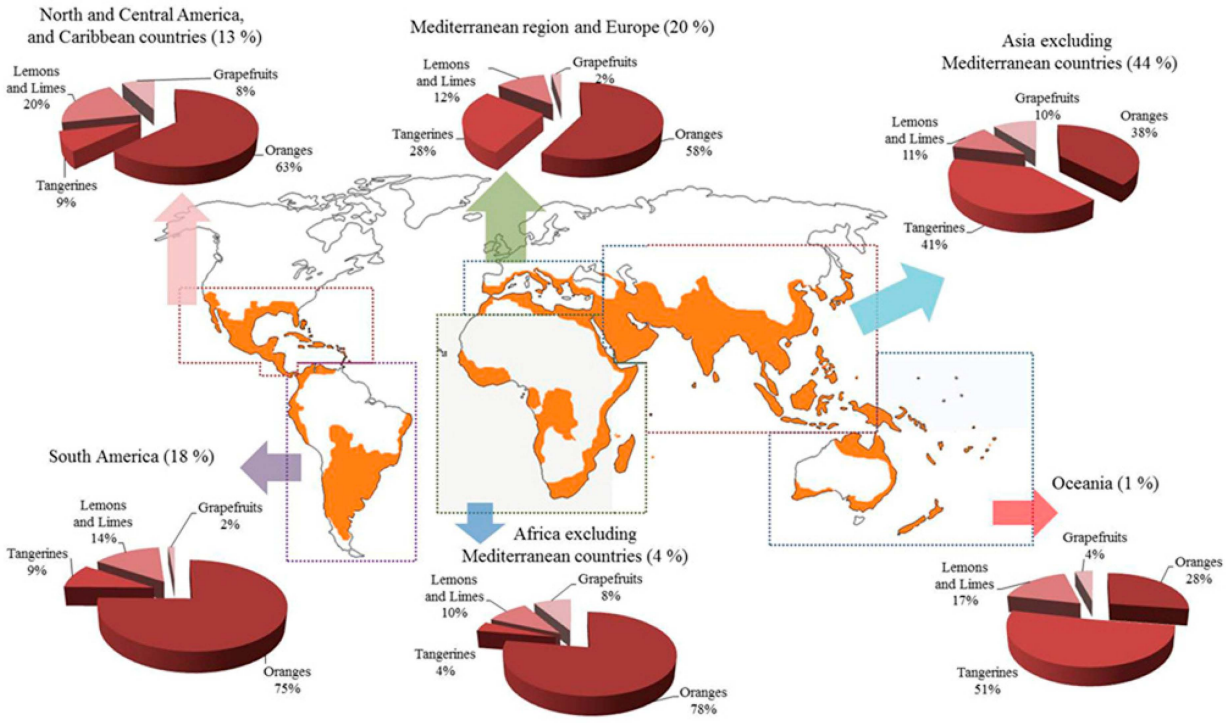

Figure 1. World main citrus growing zones and their annual productions. This figure has been reproduced from Mahato *et al.* under the terms of the Creative Commons Attribution 4.0 International license (CC-BY-4.0)[9].

compile the review. Information on nutritional composition, medicinal uses, phytochemical and pharmacological properties of *C. reticulata* was gathered from textbooks, theses and online research articles from databases such as Elsevier, Google Scholar, Scopus, Science Direct, SciFinder, PubMed, BMC, and Web of Science. These data sources were chosen based on the topic covered and the main search key terms included "taxonomy, botany, distribution, nutritional composition, ethnobotanical uses, biological and chemical properties" in relation to *C. reticulata*. Search terms were set to be in the title, keywords and abstract. To avoid too much filtering of literature, the terms were searched individually. Focusing, on its multipurpose roles, *C. reticulata* production and utilization can be a catalyst for the development of rural households and community livelihoods. It is therefore imperative to document its nutritional composition, medicinal use and pharmacological properties. With more people becoming nutrition-conscious, demand for citrus fruits and their by-products has grown even in developing countries.

Nutritional composition

Mandarin is a rich source of vitamins C and A, proteins, dietary fibres and essential minerals such as calcium, potassium, phosphorus and magnesium. Also, they contain minute quantities of vitamins B1, B2, B3, B5, B6, B9 and E[8,13]. On average, 100 g of mandarin orange consists of 85% water (85.2 g), 13% carbohydrates (13.34 g), 0.81 g protein, 0.38 g dietary fibre and 0.31 g fat[8,13]. Table 1 shows the nutritional composition of raw mandarins.

The sugars, acids, carotenoids, polyphenols, limonoids and vitamins in *C. reticulata* determine the flavour of the fruit. The vitamins, fibre and health-boosting plant compounds like flavonoids provide many health benefits to humans who eat

Table 1. Nutritional value of raw mandarins. The table has been reproduced with permission from Liu *et al.*[8].

Nutrient	Content in 100g	Nutrient	Content in 100g
Energy	53 kacl/222 kJ	Vitamin A	34 µg/ 681I.U.
Proteins	0.81 g	Vitamin E (alpha-tocopherol)	0.20 mg
Carbohydrates	13.34 g	Vitamin C	26.7 mg
Sugars	10.58 g	Vitamin B1 (Thiamin)	0.058 mg
Ash	0.38 g	Vitamin B2 (Riboflavin)	0.036 mg
Dietary fibre	1.8 g	Vitamin B3 (Vitamin PP, Niacin)	0.376 mg
Total Lipids (Fats)	0.31 g	Vitamin B6	0.078 mg
Total saturated fatty acids	0.039 g	Folate (Vitamin B9)	16 µg
Total monosaturated fatty acids	0.060 g	Choline	10.2 mg
Total polysaturated fatty acids	0.065 g	Pantothenic acid (Vitamin B5)	0.216 mg
Omega 3 (n-3) fatty acids	0.018 g	beta-Cryptoxanthin	407 µg
Omega 6 (n-6) fatty acids	0.047 g	alpha-Carotene	101 µg
Calcium	37 mg	beta-Carotene	155 µg
Iron	0.15 mg	Betaine	0.1 mg
Magnesium	12 mg	Cholesterol	0 mg
Phosphorus	20 mg	Phytosterols	-
Potassium	166 mg	Xanthophylls	138 µg
Sodium	2 mg		
Zinc	0.07 mg		
Copper	0.042 mg		
Manganese	0.039 mg		
Selenium	0.1 µg		

the fruits and related by-products. For example, the vitamin B complex helps prevent infections, helps promote cell health, energy levels, proper nerve functions, hormone and cholesterol production, and cardiovascular health. In particular, mandarin fruits are rich in β-cryptoxanthine, xanthophyll with pro-vitamin A activity[31].

Mandarins are well-accepted by consumers owing to their pleasant flavours and abundant phytochemicals. With more people becoming nutrition-conscious, there has been a growing demand for citrus fruits like mandarins, and their by-products[13].

Chemical constituents

The chemical constituents of *C. reticulata* peel, juice and fruit are shown in Table 2. The peel has high magnesium and carotenoid content[32]. Methyl-N-methyl anthranilate, a natural antinociceptive compound, has been isolated from mandarin leaves[33]. Secondary metabolites such as terpenoids, flavonoids and phenolics compounds act as deterrents to insects and microbial attack[34].

Essence oil and aroma

Mandarin is a source of essential oils which are characterized by a fresh-juice fragrance that is widely used in citrus juice products as a natural flavoring agent[8,35]. The essential oils contain volatile compounds, mainly aldehydes, limonene, ketones, esters, alcohols, terpenes, β-myrcene, 3-carene and α-pinene which provides the distinctive aromas and tastes of citrus fruits[1,36,37]. Limonene, preceded by γ-terpinene, p-cymene, alpha-pinene and myrcene, is the most abundant compound in mandarin essential oil[1,38–43].

The essential oils are greatly utilized as fragrance materials in beverages, foods, medical formulations, perfumery, toiletries and other cosmetic products[44]. To some extent, they can also be used as traditional medicine[2,9,45]. The Chinese use the dried peel of the fruit in the regulation of ch'I (energy/vitality) and to enhance digestion. The leaves and juvenile twigs are a source of essential oil called 'petitgrain oil'[23].

Medicinal uses

The edible part of the raw mandarin fruit possesses antioxidants such as vitamin C, carotenoids and phenolic compounds. The fruit is also a rich source of amino acids, sugars, organic acids, amino acids, pectins, minerals and volatile organic compounds[46–51]. These constituents are essential for the proper functioning of the body by protecting it against chronic diseases and providing basic nutrition[52]. The dietary fibre and phenolic compounds in mandarins are useful in the formulation of functional foods[32]. Mandarin fruit also contains coumarins, for instance, bergapten which sensitizes the skin to sunlight[53].

The fruit has been reported to possess laxative, aphrodisiac, antiemetic, astringent and tonic properties[54,55] while the fruit peel regulates skin moisture, softens hard and rough skin and cleanses oily skin[56]. Traditionally, it is also used as a stomachic and carminative[56–58]. Both the pericarp and endocarp are anticholesterolemic, analgesic, antiseptic, antiasthmatic,

Table 2. Chemical constituents of *C. reticulata*.

Part	Constituents	References
Peel	Fat, protein, ash, magnesium, carotenoids, dietary fibre and polyphenols	32
Juice	Beta-cryptoxanthin xanthophyll esters (zeaxanthin and lutein)	59
	Carotenoids, such as beta-cryptoxanthin.	60,61
Seed	Limonoids, including obacunone 17 beta-D-glucopyranoside, nomilinic acid 17 beta-D-glucopyranoside, limonin, nomilin, and a limonoid glucoside mixture.	62
Fruit	Alkaloids, flavonoids, tannins, phenols and saponins	34
Hexane leaves extract	Alkaloid, carbohydrate, cardiac glycosides and terpenoid	63
Methanol leaves extract	Carbohydrate, cardiac Glycosides	63
Ethanol leaves extract	Alkaloid, carbohydrate, cardiac glycosides and protein	63
Ethanol extract of the aerial part	Carbohydrates, phytosterols, flavonoids, leucoanthocyanins, and tannins	64
Methanol extract of the air-dried fruit peels	n-hexacosanoic acid, reticulataursenoside, citrusterylarachidate and citruslanosteroside	56
Ethanol extracts of the fruit peel	Saponins, tannins, cardiac glycosides, carbohydrates, reducing sugars, compound reducing sugars, terpenoids, flavonoids and sterols.	65
	Carbohydrates, amino acids, flavonoids, steroids, tannins and phenolic derivatives.	66

anti-inflammatory, antiscorbutic, antitussive, carminative, expectorant and stomachic[57,67]. Therefore, they are used in the treatment and management of dyspepsia, gastro-intestinal distension, cough with profuse phlegm, hiccup and vomiting[58,67]. The unripened green exocarp is used in the treatment of chest pains and hypochondrium, gastro-intestinal distension, swelling of the liver and spleen and cirrhosis of the liver. The seed is analgesic and carminative, thus used in the treatment of hernia, lumbago, mastitis and pain or swellings of the testes[67].

Pharmacological properties of *C. reticulata*

Antimicrobial properties

The ethanolic extract of mandarin fruit shell, a traditional herbal medicine used for gastric ulcer treatments in China, showed activity against five clinical strains of *Helicobacter pylori* at the minimum inhibitory concentration (MIC) close to 60 µg/mL[68]. The essential oil of this plant has shown antimicrobial activity with the zone of inhibition varying from 9.16 to 27.63 mm against *Escherichia coli*, *Listeria innocua*, Methicillin-Resistant *Staphylococcus aureus, S. aureus* and *Candida albicans*[43]. In a comparative study, the peel ethanol extract of *C. reticulata* inhibited the growth of all the Gram-positive bacteria tested, with the highest zone of inhibition of 20.33 ± 1.527 mm against *Bacillus* spp. However, the juice extract showed more activity against the Gram-negative bacteria with a maximum zone of inhibition of 11.33 ± 1.154 mm against *Klebsiella pneumonia*[69]. Zainab *et al.*[70] also reported that the peel extract of *C. reticulata* exhibited a high zone of inhibition against *S. aureus* (28 mm) while *E. coli*, *S. typhi* and *P. aeruginosa* showed resistance to the peel extracts. The presence of flavanones in the peel of *C. reticulata* could be responsible for the efficacy of the peel extract than that of the juice[71]. Yashaswini and Arvind[72] carried out a study to determine the antibacterial potential of *C. reticulata* var. Kinnow peel extracts against pathogenic strains of *S. aureus, E. coli, P. aeruginosa* and *K. pneumonia.* The acetone extract inhibited the growth of *K. pneumonia* and *E. coli* with a MIC value of 68.75 µg/mL and maximum zone of inhibition of 7.93 mm and 7.75 mm against *K. pneumonia* and *E. coli* respectively.

Sultana *et al.*[57] have reported that the volatile oil of *C. reticulata* peel possesses antimicrobial activities against *Escherichia coli, Staphylococcus aureus, Aspergillus flavus, Aspergillus niger, Aspergillus fumigatus,* and *Candida albicans*. Thus, suggested that the volatile oil could be useful for the treatment of skin disorders and the therapy can be incorporated into the cosmetic formulation. Based on the findings of this review, the essential oil, juice and peel extracts of *C. reticulata* may possess beneficial antibacterial agents that can be exploited in controlling unwanted bacterial infections. The peel oils of mandarins exhibit toxic insecticidal and antibacterial properties[8].

Anticancer activity

Kang *et al.*[73] have reported that the methanol extracts (100 g/mL) of *C. reticulata* peel showed increased apoptosis on SNU-C4, human colon cancer cells through Bax-related *caspase-3* activation, thus, suggested the use of *C. reticulata* on colon cancer patients. In an *in vitro* study, two flavone glucosides isolated from the mandarin fruit peel showed differentiation-inducing activity in mouse myeloid leukaemia cells (M1), and the cells exhibited phagocytic activity[74]. In addition, hexane and dichloromethane bark extracts of *C. reticulata* assayed against human lung adenocarcinoma cell line A549, human breast adenocarcinoma cell line MCF7, human Caucasian prostate adenocarcinoma cell line PC3, and one normal human prostate cell line PNT2 revealed that the extracts possess good apoptosis-inducing activity against the human cancer cell lines. Thus, the authors concluded that the hexane or dichloromethane extract of the bark of *C. reticulata* is a good crude drug treatment against lung, breast and prostate cancer. However, further *in vitro* and *in vivo* testing would be required before any recommendation of this drug can be given[75].

The anticancer potential of *Citrus medica* (2 morphotypes), *C. sinensis, C. maxima, C. limon* and *C. reticulata* peels were investigated using *in vitro* assays and *in vivo* cancer models[76]. The finding depicted that both the extracts and EOs of *C. reticulata* peels had significant activity against Dalton's Lymphoma Ascites (DLA) cell line in an MTT assay. The peel oil showed 91.9% and 100% cell death at 25 and 50 µg/mL, respectively, while the water extract showed 49.8% cell death at 5 µg/mL and 100% cell death at 25 and 50 µg/mL respectively. The *in vivo* study revealed that mice pre-treated with *C. reticulata* peel extract were significantly (50%) protected from DLA compared to post-treated mice (33%) without any obvious toxic symptoms. The volatiles (essential oils, limonoids) and non-volatiles (mainly polymethoxy flavones) in *Citrus* peels have been recognized as their bioactive/anticancer constituents[76,77].

The antiproliferative activity of limonoids extracted from *C. reticulata* was evaluated against a series of human cancer cell lines[62]. Limonoids exhibited significant growth inhibitory effects at high concentration of 100 µg/mL against human breast cancer cell lines (MCF-7). However, it could not inhibit leukaemia (HL-60), ovary (SKOV-3), cervix (HeLa), stomach (NCI-SNU-1) and liver (Hep G2) cancer cells lines[62].

Neuropharmacological activities

Gbaj *et al.*[78] evaluated the anxiolytic potentials of methanol and aqueous peels extracts of *C. reticulata* in Libya using an elevated plus-maze. The result revealed that the peel extracts exhibited significant anxiolytic activity. In addition, the anxiolytic effect of naringin has been confirmed in 6-8 weeks old mice weighing 30 to 35 g[79].

Antigenotoxicity effects

Hassan *et al.*[64] investigate the protective effect of the ethanol extract of the aerial part of *C. reticulata* cultivated in Saudi Arabia against genotoxicity induced by benzo(a)pyrene (BaP) in mice using the comet assay. In the mice treated with BaP, there was a significant increase in the DNA fragmentation in the liver tissues of male mice and an increased rate of DNA damage in mice blood cells. However, the liver and blood cells of the mice treated with ethanol extract demonstrated significant protection by inhibiting the rate of DNA damage. It was concluded that the aerial part of *C. reticulata* could be useful to reduce the genotoxicity induced by hazardous chemical agents[64]. The presence of flavonoid compounds and various secondary

metabolites could be responsible for the protective effect, pharmacological and therapeutic properties of *C. reticulata*[80–82].

Antioxidant effects

Boudries *et al.*[43] investigated the antioxidant activities of *C. reticulata*, *C. reticulata* cultivar Wilking and *C. clementine* from Algeria using 1,1-diphenyl-2-picrylhydrazil (DPPH) and reducing power. The essential oil (EO) of *C. reticulata* exhibited the strongest DPPH free radical-scavenging activity in a dose-dependent manner, followed by clementine and wilking EOs. Also, in a concentration-dependent manner, the EO of *C. reticulata* showed the greatest reducing power followed by wilking and clementine EOs. According to Junior *et al.*[83], the antioxidant nature of the citrus essential oils in terms of free radical scavenging may be due to the antioxidant activity of limonene, which was the main constituent of the oil. The peel of *C. reticulata* was evaluated for antioxidant activity, the results displayed prominent, concentration-dependent free-radical scavenging activity on stable DPPH free radicals and reactive hydroxyl radicals[84].

Also, the fruit peel of *C. reticulata*, *Zingiber officinale* and *Sesamum indicum* were investigated for their antioxidant activities using the DPPH radical scavenging technique. The findings revealed that *Z. officinale* had the highest antioxidant activity followed by *C. reticulata*, and *S. indicum*. The antioxidant activity of these plants could be attributed to a wide variety of constituents, such as the flavonoid content which are considered as major biological antioxidants[85].

Cardiovascular effects

Rincon *et al.*[32] suggested the use of tangerine peel in reducing the risk of cardiovascular diseases and some associated with lipid oxidation.

Hepatoprotective activity

The protective effect of the essential oils of *C. reticulata* on isoniazid induced hepatotoxicity in Wistar rats was investigated[86]. About 50 gm/kg, p.o. of isoniazid was administered for 30 days in order to induced liver damage in the rats. A total of 200 mg/kg, p.o.of the essential oil was administered daily for 30 days, while the standard group received Liv52[86]. The result revealed a significantly elevated level of ALT, AST, bilirubin and a decreased total protein content in the rats treated with only isoniazid as compared to the group that do not received isoniazid. However, a significant reduction in all the biochemical parameters was observed in the rats treated with the essential oil and Liv52[86].

CYP450 effects

In an *in vitro* study, the effect of tangeretin (a flavonoid isolated from tangerine juice) on hydroxylation of midazolam, a CYP3A4 probe was evaluated using human liver microsomes and recombinant CYP3A4. The finding revealed that tangeretin is a potent and regioselective stimulator of midazolam 1'-hydroxylation and complementary DNA-expressed CYP3A4[87]. However, further studies are required as the authors have indicated that tangerine juice might not have a clinical effect on CYP3A-mediated drug metabolism in humans.

Antihypercholesterolemic effects

Omer *et al.*[65] investigated the antihypercholesterolemic potential of the crude ethanolic extracts of *C. reticulata* fruit peel in an *in vivo* study. The findings revealed that daily administration of 250 mg/kg and 500 mg/kg doses of the extracts to the albino rats for four weeks produced a reduction in serum low-density lipoprotein-cholesterol, total cholesterol and triglycerides levels. Also, a significant elevation in serum high-density lipoprotein-cholesterol was observed, thus, indicating their cardioprotective effects and potential as therapeutic antihypercholesterolemic agents[65]. Hence, the efficacy of *C. reticulata* peels extracts on the observed lipid profile parameters might be attributed to the presence of polymethoxylated flavones which occur in the fruit peels.

Anti-ageing potential

According to a study by Apraj and Pandita[66], both hot and cold alcoholic extracts of *C. reticulata* exhibited strong anti-collagenase and anti-elastase activity, indicating its anti-ageing ability. However, further study is required to determine whether the extracts can be incorporated into skincare products as anti-wrinkle agents.

Toxicity

The oral administration of *C. reticulata* extracts up to 200 mg/kg has been reported to be safe[78]. Also, Li *et al.*[68] reported that a single oral dose of 16 g/kg of naringin does not produce acute oral toxicity in rats.

Other uses

Worldwide, the mandarin fruit is eaten as fresh produce[88]. It is peeled and eaten plain, used in salads, desserts and main dishes or cooked in puddings, cakes and confectionery. The peel, pulp and seeds are often discarded as waste or they can be processed into animal feed[88].

Many by-products, including pectin, dried pulp, molasses, marmalades, candied peel, peel seasoning, purees, beverage bases, alcohol, bland syrup, citric acid, seed oil and flavonoids can be obtained from mandarin fruits[4,36,89]. The dried peel or rind has a sweet-spicy flavour often used as a flavouring in cakes[4] or as a spice for cooking, baking, drinks or candy[90]. Rind powder extract, a rich source of phenolic compounds having free radical scavenging activity can be used as an anti-oxidant in meat products[88].

Conclusion

C. reticulata is an important plant which contains some compounds and nutritional values that are of great health importance. The fruit is rich in antioxidants and phenolic compounds, sugars, organic acids, amino acids, pectins, minerals and volatile organic compounds. These substances are essential for the proper functioning of the body by protecting it against chronic diseases, provides basic nutrition and useful in the formulation of functional foods. Based on research carried out, the fruits and peels of *C. reticulata* have been reported to possess neuropharmacological, hepatoprotective, anticancer, antimicrobial, antigenotoxicity, antioxidant activities, antihypercholesterolemic and cardiovascular effects. The usage

of *C. reticulata* was shown to be broad, ranging from dietary applications to the treatment of terminal medical conditions, thus, it is imperative to carry out more research on the toxicity of this plant. Since the peels contain bioactive constituents of pharmacological importance, further investigations should be conducted to investigate whether it could be boiled and consumed orally, establish dosage ranges for safe consumption and evaluate target-organ toxicity.

Data availability

Underlying data

No data are associated with this article

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