Chaenomeles speciosa: A review of chemistry and pharmacology

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Abstract. *Chaenomeles speciosa* (Sweet) Nakai (*C. speciosa*, Rosaceae family) is an effective medicinal plant, which has long been used in China to treat various diseases, such as rheumatism, cholera, dysentery, enteritis, beriberi and vitamin C deficiency syndrome. A series of chemical constituents, including triterpenoid, phenolic and phenylpropionic acids, flavonoids, saccharides, essential oils and alkaloids, have been isolated from this plant and some have already been evaluated for their biological activities. Pharmacological investigations demonstrated that *C. speciosa* possesses anti-inflammatory, antinociceptive, antimicrobial, antioxidant, immunoregulatory, antiparkinsonian, hepatoprotective and antitumor properties. The objective of this review was to summarise available up-to-date and comprehensive information on *C. speciosa* and provide a relevant reference for further investigations.

Contents

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1. Introduction

Chaenomeles speciosa (Sweet) Nakai (*C. speciosa*, Rosaceae family), also referred to as mugua, tiegenghaitang, tiejiaoli or zhoupimugua, is distributed in Central, East and Southwest China and is now cultivated worldwide. According to the Chinese Pharmacopoeia (2010 edition), the plant cultivated in Anhui, China, is the genuine medicinal material and is considered to be of the highest quality. According to traditional Chinese medicine, the fruit of *C. speciosa*, which is warm in nature and sour in flavor, has the ability to calm the liver, relax the muscles and tendons, harmonize the stomach and eliminate dampness (1), which may prevent and cure several clinical conditions, such as rheumatism, cholera, dysentery, enteritis, beriberi, vitamin C deficiency syndrome, neuralgia, migraine, stroke and depression (2-6).

Due to the extensive medicinal applications of *C. speciosa*, numerous phytochemical and pharmacological studies have been conducted. The aim of this review was to summarize the published scientific information that were accumulated over the last decades regarding this important Chinese medicinal plant for further investigation.

2. Chemical constituents

Several compounds have been isolated from *C. speciosa* (mainly its fruits), including triterpenoid, phenolic and phenylpropionic acids, flavonoids, saccharides, essential oils and alkaloids. Oleanolic and ursolic acids, of the triterpenoid acid family, are the characteristic chemical markers of *C. speciosa* and may be used to evaluate the quality of the plant. In addition, *C. speciosa* is rich in nutritional constituents beneficial to the human body (7). The main compounds are listed in Table I. The chemical structures of triterpenoid acids are presented in Fig. 1.

3. Anti-inflammatory and antinociceptive effects

C. speciosa has long been used for the treatment of rheumatoid arthritis in China and has been shown to possess anti-inflammatory and antinociceptive properties (8-14).

Table I. Compounds isolated from *Chaenomeles speciosa*.

Type	Compound name (refs.)	Plant part
Organic acids		
Triterpenoid acids	Oleanolic acid (60,61)	Fruit and leaf
	Ursolic acid (62)	Fruit
	Betulinic acid	Fruit
	3-*O*-acetyl ursolic acid	Fruit
	3-*O*-acetyl pomolic acid (63)	Fruit
	Speciosaperoxide	Fruit
	Maslinic acid	Fruit
	Tormentic acid (64)	Fruit
Phenolic acids	Protocatechuic acid	Fruit
	Gallic acid (65)	Fruit
	2'-Methoxyaucuparin	Fruit
	p-Hydroxybenzoic acid (66)	Fruit
	3,4-dihydroxybenzoic acid (69)	Fruit
	4-Hydroxy-3-methoxy-benzoic acid (67)	Fruit
Phenylpropionic acids	Cinnamic acid	Fruit
	Chlorogenic acid	Fruit
	Caffeic acid (66)	Fruit
	Phenyllactic acid (62)	Fruit
Others	5-(3-Methylphenyl)pentanoic acid	Fruit
	Butenedioic acid	Fruit
	Butanedioic acid	Fruit
	Benzoic acid	Fruit
	2-Hydroxylbutanedioic acid	Fruit
	Citramalic acid	Fruit
	Benzeneacetic acid	Fruit
	Nonanoic acid	Fruit
	4-Methoxylbenzoic acid	Fruit
	(Z)-3-Phenyl-2-propenoic acid	Fruit
	Nonanedioic acid	Fruit
	3-(4-Methoxylphenyl)2-propenoic acid	Fruit
	Octadecanoic acid	Fruit
	Hexadecanoic acid	Fruit
	Methyl-16-heptadecanoic acid	Fruit
	Octadecatrienoic acid (68)	Fruit
	Ethanedioic acid	Fruit
	Propandioic acid	Fruit
	Furancarboxylic acid	Fruit
	4-Oxo-pentanoic acid	Fruit
	3-Hydroxy-heptanoic acid	Fruit
	3-Hydroxy-hexanoic acid	Fruit
	2-Ketoglutaric acid	Fruit
	cis-Aconitic acid	Fruit
	Citrate	Fruit
	4-Oxo-pimelic acid	Fruit
	(E)-2-butenedioic acid	Fruit
	Methoxy-butanedioic acid	Fruit
	3-Hydroxy-4-methyl-pentanoic acid	Fruit
	N-acetyl-L-aspartic acid	Fruit
	15-Octadecenoic acid	Fruit
	(Z)-9-octadecenoic acid (67)	Fruit
Flavonoids	Quercetin (69)	Fruit
	Rutin (70)	Fruit
Essential oils	Hexanal	Fruit
	Ethyl butyrate	Fruit
	(E)-2-hexenal	Fruit
	(Z)-3-hexenyl acetate	Fruit
	Ethyl hexanoate	Fruit
	Linalool	Fruit
	trans-Linalool oxide (furanoid)	Fruit
	cis-Linalool oxide (furanoid)	Fruit
	α-Terpineol	Fruit
	Ethyl octanoate	Fruit
	Edulan I	Fruit
	Ethyl(Z)4-decenoate	Fruit
	Ethyl p-methoxybenzoate (71)	Fruit
	Benzaldehyde	Fruit
	Linaloyl oxide	Fruit
	n-Octanal	Fruit
	α-Terpinene	Fruit
	ϱ-Cymene	Fruit
	Limonene	Fruit
	1,8-Cineole	Fruit
	(Z)-β-Ocimene	Fruit
	(E)-β-Ocimene	Fruit
	γ-Terpinene	Fruit
	n-Octanol	Fruit
	(+)-4-Carene	Fruit
	ϱ-Cymenene	Fruit
	trans-Limonene oxide	Fruit
	n-Nonanal	Fruit
	Iso-3-thujanol	Fruit
	ϱ-Menth-3-3-en-8-ol	Fruit
	Menthol	Fruit
	Borneol	Fruit
	Terpinen-4-ol	Fruit
	n-Decanal	Fruit
	trans-2-Decenal	Fruit
	Carvenone	Fruit
	Bornyl acetate	Fruit
	ϱ-Menth-3-3-en-8-ol acetate	Fruit
	α-Longipinene	Fruit
	β-Elemene	Fruit
	Longifolene	Fruit
	β-Caryophyllene	Fruit
	Neryl acetone	Fruit

Table I. Continued.

Type	Compound name (refs.)	Plant part
	E-Ethyl cinnamate	Fruit
	(E,E)-α-Farnesene	Fruit
	Germacrene A	Fruit
	δ-Amorphene	Fruit
	E-Nerolidol	Fruit
	γ-Eudesmol	Fruit
	Epi-α-Cadinol	Fruit
	α-Cadinol (31)	Fruit
Others	3β-acetoxyurs-11-en-13β,28-olide	Fruit
	Reseoside	Fruit
	Vomifoliol	Fruit
	(6*S*,7*E*,9*R*)-6,9-dihydroxy-4,7-megastigmadien-3-one-9-*O*-[β-D-xylopyranosyl(1→6)-glucopyranoside] (64)	Fruit
	Ethyl chlorogenate	Fruit
	Kojic acid (65)	Fruit
	2-Hydroxyl-butanedioicacid-4-methyl ester	Fruit
	Esculetin (62)	Fruit
	Hydroquinone	Fruit
	Methyl 3-hydroxylbutanedioic ester (69)	Fruit

Several triterpenoids, such as oleanolic, ursolic, betulinic and maslinic acids, possess anti-inflammatory properties (15-18). Previous studies investigated the anti-inflammatory effects of oleanolic acid on adjuvant-induced rat arthritis and carrageenan-induced rat paw edema (19,20). Oleanolic and ursolic acids display anti-inflammatory activity through the direct inhibition of secretory phospholipase A2 (sPLA2) and formation of sPLA2-oleanolic (ursolic) acid complex (21-22). Oral administration of ursolic acid at doses of 10, 20, 40, 80 and 160 mg/kg was shown to downregulate the production of interleukin (IL)-2, interferon-γ and tumor necrosis factor α (TNF-α) (23). Oleanolic and ursolic acids were also shown to suppress the inflammatory cytokine-induced E-selectin expression in endothelial cells via inhibition of nuclear factor-κB (NF-κB) activation (24). Betulinic acid exerts potent inhibitory effects on vascular inflammatory processes induced by TNF-α in human umbilical vein endothelial cells, through the direct inhibition of reactive oxygen species generation and NF-κB activation (25). Maslinic acid was shown to suppress cyclooxygenase-2 expression in Raji cells, partly via the NF-κB and activator protein-1 signaling pathways (26).

To evaluate the anti-inflammatory properties of the glucosides isolated from *C. speciosa* (GCS), the collagen-induced arthritis (CIA) rat model was used. The GCS (30, 60, 120 mg/kg, ig x 7 days) significantly suppressed the inflammatory response, restored body weight and the weight of immune organs of CIA rats. GCS also reduced lymphocyte proliferation and IL-1, -2 and TNF-α production in peritoneal macrophages and synoviocytes in CIA rats. Furthermore, GCS were shown to inhibit the mRNA expression of G-protein (Gi) and TNF-α of synoviocytes and increase the mRNA expression of G-protein (Gs) of synoviocytes in CIA rats. The administration of GCS at concentrations of 0.5, 2.5, 12.5, 62.5, 125 mg/l were shown to increase the cAMP levels in the synoviocytes of CIA rats *in vitro*. The anti-inflammatory and immunoregulatory activities of the GCS are mediated through G-protein-adenylate cyclase-cAMP transmembrane signal transduction in synoviocytes (8). The GCS (60 and 120 mg/kg, ig x 8 days) were able to dose-dependently inhibit secondary inflammatory paw edema, pain response and polyarthritis index in rat adjuvant arthritis (AA) induced by Freund's complete adjuvant. The ultrastructural changes of synoviocytes were improved and the production of IL-1, TNF-α and prostaglandin E_2 (PGE_2) was suppressed in AA rats (9). The GCS (60 and 120 mg/kg) were also reported to downregulate the level of serum antibodies in rats with AA (27). The anti-nociceptive bioactivity of the GCS may be evaluated by acetic acid writhing, mouse formalin and arthritic flexion tests. The GCS (60, 120, 240 mg/kg for mice and 30, 60, 120 mg/kg for rats, ig) were shown to reverse all the changes in the responses mentioned above, which is likely associated with their inhibitory effects on peripheral inflammatory mediators (10).

In addition, the 10% ethanol fraction, polysaccharides, saponins and total flavonoids isolated from *C. speciosa* were also shown to possess anti-inflammatory and analgesic properties. The 10% ethanol fraction exhibits more potent anti-inflammatory effects compared to other fractions at the same dose. Chlorogenic acid, contained in this fraction and identified by high-performance liquid chromatography, may be responsible for this anti-inflammatory effect (12). The polysaccharides may inhibit the development of primary and secondary arthritis in AA mice, which is possibly associated with the suppression of lymphocyte proliferation and regulation of inflammatory cytokines (14). The saponins from *C. speciosa* may relieve the symptoms in AA rats, inhibit the immunoinflammatory response, reduce PGE_2 synthesis, suppress increased thymocyte T cells and diminish the $CD4^+$ T lymphocytes in the peripheral blood of AA rats (13,28). Total flavonoids were found to exhibit systemic and peripheral analgesic activity in mouse and rabbit models (11).

Three compounds, 3,4-dihydroxybenzoic acid, quercetin and methyl 3-hydroxybutanedioic ester, were shown to inhibit the production of TNF-α by 22.73, 33.14 and 37.19%, respectively. Quercetin was also shown to facilitate the release of IL-6 in RAW264.7 macrophage cells (29).

4. Antimicrobial activity

C. speciosa has been traditionally used for the treatment of diarrhea in China. The extract of *C. speciosa* was proven to inhibit heat-labile enterotoxin (LT)-induced diarrhea in mice via blocking the binding of the B subunit of LT (LTB) to the ganglioside G_{M1} [Galβ1-3GalNAcβ1-4 (Neu5Acα2-3) Gal-β1-4Glc-ceramide]. The ethyl acetate (EA) and n-butanol soluble fractions were confirmed to be the most active, eliminating the interactions between LTB and G_{M1}. Oleanolic, ursolic and betulinic acids from the EA fraction are considered as the major therapeutic agents in the treatment of LT-induced diarrhea. These compounds bind to LTB via hydrogen bonds and hydrophobic contacts with amino acid residues of LTB by docking techniques (30). The essential oil extracted from

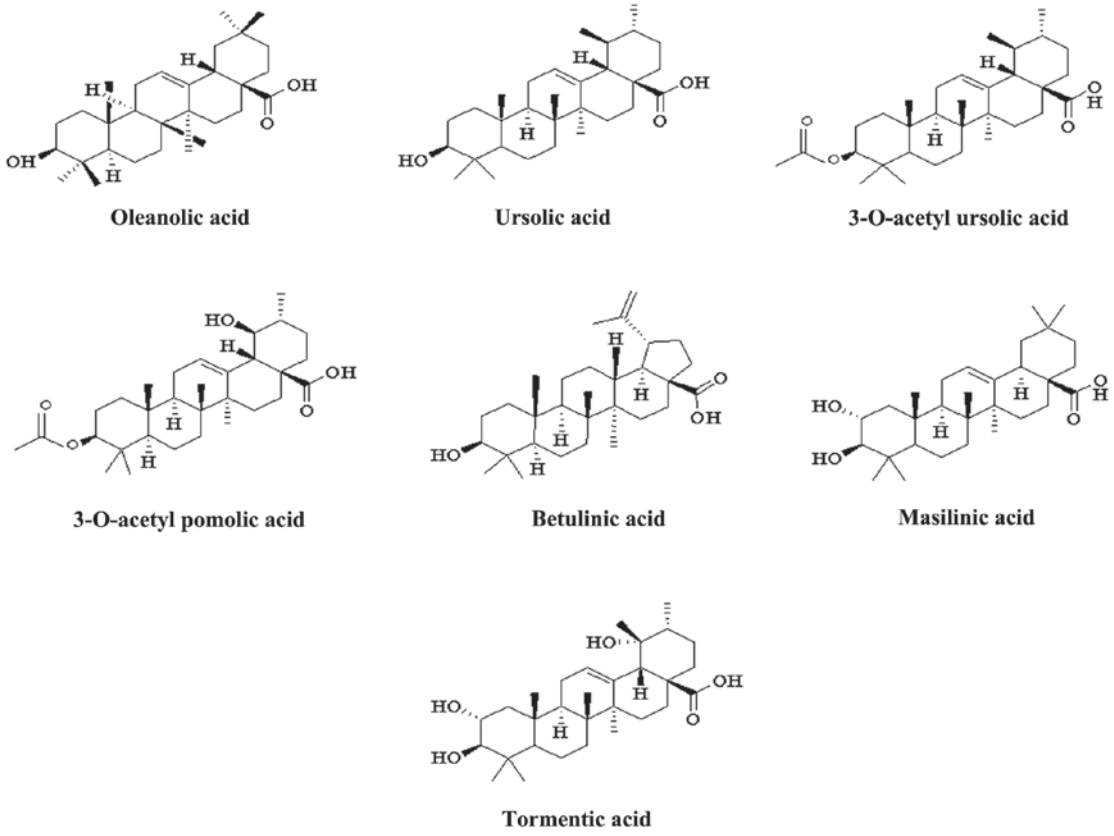

Figure 1. Chemical structure of the main triterpenoid acids from *Chaenomeles speciosa*.

C. speciosa exhibits a broad spectrum of antimicrobial activity and is more potent against gram-positive compared to gram-negative bacteria in the disc diffusion and broth microdilution tests (31). The avian influenza virus may cause oxidative stress and severe inflammation; 3,4-dihydroxybenzoic acid, quercetin and methyl 3-hydroxybutanedioic ester isolated from *C. speciosa* may act synergistically in the treatment of avian influenza and are a potential source of antiviral agents (29). The ethanol extract of *C. speciosa* exhibits potent antibacterial activity, with a minimal inhibitory concentration of 0.125 mg/ml and a minimal bactericidal concentration of 0.25mg/ml (32).

5. Antioxidant activity

The 80% methanol extract from *C. speciosa* inhibits tyrosinase activity, followed by suppression of melanogenesis (33). *C. speciosa* possesses significant antioxidant properties, partly due to its abundance in vitamin C and polyphenols. The *C. speciosa* powder processed by a specific method exhibits good scavenging activity against 1,1-diphenyl-2-picrylhydrazyl free radical (DPPH) and O_2^-, with a scavenging index of 945±20 μg DPPH/g and 700±21 U/ml, respectively. and a ferric reducing antioxidant power of 173±7 μmol Fe^{2+}/g. *C. speciosa* may considerably reduce the serum levels of low-density lipoprotein cholesterol and total cholesterol, increase glutathione peroxidase activity and decrease the relative atherosclerotic plaque area of the aortic sinus and aortic arch in $ApoE^{-/-}$ mice (34). The total flavonoids from *C. speciosa* were shown to significantly reduce the peroxide value in lard, clear DPPH and deoxidize Fe^{3+} in a dose-dependent manner, exhibiting a more potent antioxidant effect compared to that of vitamin C (35). In addition, 3,4-dihydroxybenzoic acid and quercetin isolated from *C. speciosa* exerted a more potent inhibitory effect on DPPH and neuraminidase (29).

6. Immunoregulatory effect

The GCS were shown to suppress the contact hypersensitivity (CHS) response. In mice with CHS induced by 2,4-dinitro-I-dinitroflurobenzene, GCS (120 mg/kg) exerted an inhibitory effect similar to that of the control drug 4-acetylaminophenylacetic acid on the thymus and spleen indices. The GCS were shown to inhibit splenocyte proliferation induced by concanavalin A, decrease the $CD4^+/CD8^+$ T lymphocyte ratio and restore the $CD4^+/CD8^-$ subset ratio in CHS mice. The GCS were also shown to decrease the production of IL-2 and transforming growth factor-β1 (TGF-β1) and increase the IL-4 level in the thymus of CHS mice (36). *C. speciosa* exerted a protective effect on mice with immunosuppression induced by cyclophosphamide (CTX). After the mice were administered *C. speciosa* for 15 days, the serum hemolysin and lymphocyte transformation rates improved significantly and the mRNA expression of FOXP3, TGF-β, PD1, Fas and Bax was considerably diminished compared to the CTX-group (37).

7. Dopamine transporter inhibitory and antiparkinsonian effects

C. speciosa was proven to be effective in dopamine transporter (DAT) regulation and antiparkinsonism, as determined

by *in vitro* and *in vivo* assays. In Chinese hamster ovary (CHO) cells and two animal models [6-hydroxydopamine (6-OHDA)-lesioned rats and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice], the aqueous extract of *C. speciosa* was found to markedly inhibit dopamine uptake by CHO cells and synaptosomes at concentrations of 1-1,000 μg/ml in a concentration-dependent manner; however, it had little effect on norepinephrine transporters at concentrations up to 1,000 μg/ml and no effect on γ-aminobutyric acid or serotonin transporters. The aqueous extract of *C. speciosa* was shown to alleviate 1-methyl-4-phenylpyridinium-induced toxicity in CHO cells stably expressing DAT. In neurobehavioral studies, the extract time-dependently mitigated 6-OHDA-induced hemi-parkinsonian rotations in rats and dose-dependently attenuated MPTP-induced deficits in mice during endurance performance. The aqueous extract also significantly reduced the loss of tyrosine hydroxylase-positive neurons in the substantia nigra of MPTP-treated mice. The antiparkinsonian-like effects of *C. speciosa* may be associated with the suppression of DAT activity (38).

8. Agonist targeting β2-adrenoceptors

β2-adrenoceptor agonists are the most widely used agents in the treatment of asthma due to their bronchodilator actions (39). The transfected human embryonic kidney 293 cell clone was developed for screening the agonists of human β2-adrenoceptor among Chinese medicinal herbs. The ethanol extract of *C. speciosa* exerted significant activating effects on reporter gene expression at a half maximal effective concentration of 4.8 μg/ml (40).

9. Inhibitory effect on gastrointestinal smooth muscle contraction

Total flavonoids from *C. speciosa* were shown to relax gastrointestinal smooth muscles, through exerting an inhibitory effect on the contraction of the isolated rabbit gastric fundus and ileum induced by acetylcholine and $CaCl_2$ in a dose-dependent manner and suppressing the contraction of the isolated rabbit taenia coli elicited by high K^+ depolarization. These relaxant effects may be associated with the voltage-dependent Ca^{2+} channel blockade by total flavonoids (40,41).

10. Hepatoprotective effects

The 70% alcohol extract of *C. speciosa* exerts a certain protective effect on rats with chronic hepatic damnification injected with CCl_4 (42). *C. speciosa* contained in high-fat diet may prevent mice from developing non-alcoholic steatohepatitis by regulating the expression of toll-like and death receptors and the secretion of inflammatory cytokines (43). Oleanolic acid isolated from *C. speciosa* exerts a strong inhibitory effect on hepatitis B virus replication, with an inhibitory ratio of 29.33% at a concentration of 20 μg/ml (44). Oleanolic acid was shown to effectively protect the liver from acute injury induced by chemicals, as well as from fibrosis and cirrhosis precipitated by chronic liver diseases (45,46). Oleanolic acid was shown to increase the expression of hepatic metallothionein and nuclear factor E_2-related factor 2 (Nrf2) against hepatotoxicants (47), but was also found to activate Nrf2-independent cytoprotective mechanisms in Nrf2-null mice (46).

11. Antitumor activity

It was reported as early as 1975 that organic acids from *C. speciosa* exert antitumor effects in mice with Ehrlich ascites carcinoma (48); this antitumor effect is a common property of numerous triterpenoids (49,50). Among these, oleanolic, ursolic, betulinic and maslinic acids are the most notable triterpenoid compounds. When applied to estrogen receptor-negative breast cancer and osteosarcoma cells, oleanolic acid elicited tumor cell apoptosis through inhibition of mammalian target of rapamycin signaling (51,52). Oleanolic and ursolic acids also caused apoptosis in HuH7 human hepatocellular carcinoma cells via downregulation of the X-linked inhibitor of apoptotic protein (53). Oleanolic, ursolic and maslinic acids were shown to exert potent antiangiogenic effects on liver and non-small-cell lung cancer cell lines (54,55).

12. Conclusions

C. speciosa is a dual-purpose medicinal and edible plant. In terms of medicinal application, extensive pharmacological investigations demonstrated that *C. speciosa* is a bioactive species possessing anti-inflammatory, antinociceptive, antimicrobial, antioxidant and immunoregulatory properties. These pharmacological activities partly verified the rationale of the traditional application of *C. speciosa* in the treatment of rheumatism, cholera, dysentery, enteritis and beriberi.

An increasing number of studies are being conducted to investigate the phytochemistry of *C. speciosa* and a number of chemical constituents, including triterpenoid, phenolic and phenylpropionic acids, flavonoids, saccharides, essential oils and alkaloids, have been isolated from the fruit and leaves. Triterpenoid acids, oleanolic and ursolic acid in particular, are the major active constituents, which possess several pharmacological properties *in vivo* and *in vitro*, including anti-inflammatory, hepatoprotective and antitumor properties. The hepatoprotective effects of oleanolic acid allow its use as an oral medication for the treatment of liver disorders in China (56,57). Flavonoids, another main bioactive constituent of *C. speciosa*, were proven to possess antioxidant (35), antispasmodic (41,58), analgesic (11) and anti-influenza (59) properties. However, the specific ingredients of flavonoids have not been determined. Therefore, bioassay-guided isolation and identification are required for the obtained bioactive compounds.

Although various bioactivities of extracts or compounds obtained from *C. speciosa* are verified using laboratory animals or cells, few molecular mechanisms of action have been determined, which may limit further clinical application of this plant. In addition, when a drug is used in the clinical setting, its safety profile is of utmost importance. Of note, there are few toxicological evaluations reported on other extracts or compounds.

Apart from the fruit and leaves, other parts of the *C. speciosa* plant, including the seed, flower, root, branch and bark, have been clinically used as medicine. However, the number of available studies on the chemical components and

pharmacological activities of these parts is limited and further investigations are required.

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