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Cudrania tricuspidata: an updated review on ethnomedicine, phytochemistry and pharmacology

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Cudrania tricuspidata is a perennial plant of the family Moraceae with numerous medicinal and nutritional applications. It has been widely used in East Asia as an important traditional folk medicine for the treatment of many ailments such as eczema, mumps, tuberculosis, contusions, insomnia and acute arthritis. The whole plant of *C. tricuspidata*, including the roots, leaves, bark, stems and fruits, has been found to contain diverse phytochemicals, including xanthones, flavonoids, organic acids, and polysaccharides, with various bioactivities. In particular, xanthones and flavonoids, as the main active constituents, isolated from *C. tricuspidata* have been proven to possess notable anti-inflammatory, antioxidative, antitumor, hepatoprotective, neuroprotective and anti-obesity effects. This review summarizes the botany, traditional uses, phytochemistry and pharmacology of *C. tricuspidata*, and the limitations of studies on this species have also been discussed such that to serve as the basis for further research and development on this medicinal plant.

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1 Introduction

Cudrania tricuspidata (Carr.) Bur. ex Lavallee, which is a deciduous thorny tree belonging to the family Moraceae, is widespread throughout East Asia1 and is known as cudrang, mandarin melon berry, silkworm thorn, storehouse bush, hariguwa (in Japanese) and che (in Chinese).2-4 In China, C. tricuspidata roots have been used as 'Chuan-po-shi' in traditional Chinese medicine (TCM) in the treatment of gonorrhea, rheumatism, jaundice, boils, scabies, bruising, and dysmenorrhea;5,6 its root bark has been widely used in the treatment of lumbago, hemoptysis, and contusions;⁷ and its roots and stems have also been applied in the forms of syrups, granules and injections to cure tumors of the digestive tract.8 In Korea, C. tricuspidata has become one of the most ubiquitous folk remedies against cancer during the last few decades.9 In addition to the above medical uses, in China the stems and roots of C. tricuspidata have been used to prepare herbal teas or functional beverages for a long period;10 the stems, which contain a reddish-yellow dye, have been noted for their use in coloring imperial garments;³ and the tender leaves of C. tricuspidata have been used as a perfect food for breeding silkworms since the

The immense medicinal and economic value of C. tricuspidata has encouraged numerous studies of its phytochemicals and pharmacological activities. C. tricuspidata extracts have been demonstrated to possess good therapeutic effects against various ailments including inflammation, 14,15 tumors, 16,17 obesity, 18,19 and diabetes. 20,21 Xanthones and flavonoids have been considered to be the two major classes of phytochemicals in C. tricuspidata. For example, prenylated xanthones and flavonoids were found to be the most important and abundant constituents in its leaves and root bark with regard to their anti-inflammatory, 22,23 antitumor,16,24 notable atoprotective, 25,26 neuroprotective, 27,28 and anticoagulant 29 activities; hydroxybenzyl flavonoid glycosides from the stem bark were reported to be promising natural antioxidant and antitumor agents;30 and prenylated isoflavonoids and benzylated flavonoids from the fruits displayed potential antiinflammatory³¹ and antioxidant³² activities. Besides, a glycoprotein (75 kDa) from C. tricuspidata, which consisted of carbohydrate (72.5%) and protein moieties (27.5%), exhibited distinctive characteristics with anti-inflammatory,33 antioxidant,34 hepatoprotective,35 and immunomodulatory66 effects.

To date, to the best of our knowledge, no comprehensive review concerning *C. tricuspidata* has been available. A literature survey was conducted *via* an electronic search using PubMed,

Han dynasty, and the natural silk has been praised under the name of Zhe Si.¹¹ Its edible fruits have been made into juices, jams, alcoholic beverages, dietary supplements and other health products in Korea.¹² Moreover, its bark fibers have been utilized to make paper and its trunks have been used as valuable timber for furniture manufacture.¹³

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Scopus, ACS, Web of Science, ScienceDirect, China Knowledge Resource Integrated Database (CNKI), Google Scholar, Sci-Finder and a library search for ethnobotanical textbooks. The Plant List (www.theplantlist.org), the Missouri Botanical Garden's Tropicos nomenclature database (www.tropicos.org) and the Chinese Field Herbarium (www.cfh.ac.cn) were used to validate the taxonomy and also obtain information regarding subspecies and cultivars. On the basis of the literature search, we reviewed the achievements of research on the botanical characteristics, traditional uses, phytochemicals and pharmacological activities of C. tricuspidata so as to provide a systematic summary of the literature for further research on, and development of, this medicinal plant.

Botany and traditional uses of C. tricuspidata

2.1. Botany of C. tricuspidata

C. tricuspidata is one of six species in the genus Cudrania, which is endemic to Asia and Oceania, of the family Moraceae in the order Urticales.37 Five species, namely, C. tricuspidata, C. cochinchinensis (Lour.) Kudo et Masam, C. fruticosa (Roxb.) Wight ex Kurz, C. amboinensis (Bl.) Miq., and C. pubescens Trec., as well as C. cochinchinensis var. gerontogea (Nakai) Kudo et Masam, have been widely cultivated in Southern China, including Yunnan, Fujian and Jiangsu provinces, as well as in Hebei province, as profitable plants for producing valuable fruits and timber. 38,39 In Europe C. tricuspidata was introduced into cultivation in 1870, and in the USA in 1909.40 In contrast, wild populations of this species are now under threat of extinction.

As a hardy deciduous plant, C. tricuspidata is widely distributed in lowlands, foothills, forests, or dense scrub at altitudes of between 500 and 2000 m. It can eventually grow to a height of approximately 1.0-7.0 m (Fig. 1), but often exists as a broad spreading bush or small tree. Its leaves have single alternate ovate to rhombic-ovate blades with a size of 5.0-14.0 cm long and 3.0-6.0 cm wide; its flowers have a dioecious capitulum with an inflorescence length of 0.5 (male) or 1.0-1.5 cm (female); the color of its syncarpous fruits is orange-red when mature; and its roots, which are up to 50 cm long, are yellow and irregularly cylindrical.37

2.2. Traditional uses

Since ancient times, C. tricuspidata has been used as a folk medicine in oriental countries.41 The medicinal material, which is known as Zhemu in TCM, is sweet in taste, slightly warm in nature and acts on the liver and spleen meridians in TCM theory.42 Its medicinal usage was first documented in Ben Cao Shi Yi (700-800 A.D., Tang Dynasty), which is a famous masterpiece of TCM,42 followed by other Chinese medical classics such as Ben Cao Yan Yi (1116 A.D., Song Dynasty), 43 Ben Cao Hui Yan (1624 A.D., Ming Dynasty),44 and the Dictionary of Chinese Herbal Medicine (2006 Edition). Notably, C. tricuspidata roots, together with the roots of C. cochinchinensis (Lour.) Kudo et Masam, have been recorded as 'Chuan-po-shi' in the Chinese

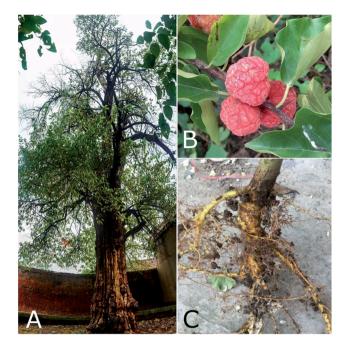


Fig. 1 Whole plant (\sim 200 years) (A), fruits (B) and roots (C) of C. tricuspidata.

Pharmacopoeia (1977 Edition).5 According to traditional applications and empirical practice, the bark of C. tricuspidata has mainly been used to strengthen the body and improve health conditions, and the trunk to invigorate the circulation of the blood and cure impaludism. 42 An aqueous decoction of its fruits and leaves (15-30 g) could be taken orally to relieve rheumatoid arthritis. Scabies and eczema could be alleviated using a decoction of its roots mixed with the roots of C. cochinchinensis and glutinous rice.45 An aqueous decoction of its roots combined with Acanthus ilicifolius L. and Desmodium pulchellum (L.) Benth, was documented to treat hepatitis, in particular viral hepatitis. 46,47 Currently, the bark of C. tricuspidata, together with Zhemu syrup (a traditional Chinese patent medicine), is widely employed in TCM clinics for the treatment of cancer of the alimentary system, in particular gastric carcinoma.8,24 Specifically, C. tricuspidata has been widely used with a long folkloric medicinal history by Chinese nationalities including Yi, Wa, Tong, Bai and Yao.

In the Korean classic Donguibogam (1613 A.D., Joseon Dynasty), C. tricuspidata was recorded as treating eczema, mumps, tuberculosis, contusions, and acute arthritis.48 Its fruits are commonly consumed in the Korean daily diet owing to diverse biological effects, e.g., antioxidant, antiinflammatory and immunomodulatory activities.12 In addition, during the last few decades, the whole plant of C. tricuspidata has been exploited as an important folk remedy for cancer in Korea.49

Phytochemistry

Over recent decades, a large number of chemical constituents have been isolated from C. tricuspidata. Xanthones and Review **RSC Advances**

flavonoids have been recognized to be the main active and structurally diverse constituents responsible for the various activities of this species, followed by organic acids, polysaccharides, phenylpropanoids, and other constituents (Table 1).

3.1. Xanthones (1-99)

The presence of abundant xanthones substituted by a variety of isoprenoid, phenolic and methoxy groups has been considered to be a taxonomic feature of C. tricuspidata (Fig. 2). 17,49,50 Among these, from the perspective of the structure-activity relationship (SAR), xanthones substituted by isoprenoid groups display better biological activities. For instance, cudratricusxanthone A (CTXA, 1), cudraxanthones L (28) and M (29), and macluraxanthone B (72) are notable isoprenylated xanthones with antiinflammatory,22 antitumor,17 neuroprotective,51 atoprotective,26 monoamine oxidase (MAO)-inhibiting,50 anticoagulant,29 antidiabetic,52 and neuraminidase-inhibiting effects.⁵³ Cudratricusxanthones B-E (2-5) and G (7), cudraxanthones D (20), L and M, and macluraxanthones B and C (73), which are classed as catecholic xanthones, could be converted into quinone methide intermediates in an enzymatic or a nonenzymatic manner⁵⁴ and were reported to have significant antitumor activity. 17,49,55,56 In addition, catecholic xanthones, specifically cudraxanthone C (19) and 1,3,7-trihydroxy-4-(1,1dimethyl-2-propenyl)-5,6-(2,2-dimethylchromeno)xanthone (84), exhibited both potent superoxide- and hydroxyl radicalscavenging activities, which could be rationalized by their chelating effect with Fe²⁺ ions.⁵⁶

It should be noted that investigations into quantitative analysis of the characteristic xanthones in C. tricuspidata are scarce. On the basis of HPLC analysis, cudratricusxanthones B, D and F (6) and macluraxanthone B in C. tricuspidata root bark were found to account for 0.017%, 0.026%, 0.025% and 0.071%, respectively.⁵⁷ The quantitative analysis of other xanthones in C. tricuspidata is worth investigating in the future.

3.2. Flavonoids (100-257)

Flavonoids account for the largest proportion of C. tricuspidata and have attracted particular interest because of their welldefined pharmacological activities. To date, more than 120 flavonoids (Fig. 2) have been isolated from C. tricuspidata and can be classified into flavones (100–128), flavanones (129–173), and isoflavones (174-257). Structurally, the majority of them possess prenylated, benzylated, and methoxy groups substituted on their aromatic rings. Cudraflavanone E (133), which is isolated from C. tricuspidata roots, features a rare flavanone skeleton with the B-ring fused to a furan ring.58 Lee et al. 16,59 isolated a series of rare benzyl-substituted flavonoids, i.e., gericudranins A-E (161-165), from C. tricuspidata. Notably, prenylated flavonoids have been regarded as attractive specialized metabolites with diverse biological activities. Specifically, cudraflavone B (104), which is a prominent prenylated flavonoid from the roots of C. tricuspidata, exhibited MAO-inhibiting, 50 antiatherosclerotic,9 anti-inflammatory,60 hepatoprotective,25 antitumor,61 and neuroprotective62 effects. Euchrestaflavanones

B (143) and C (144) displayed antibacterial activity against Gram-positive bacteria, Staphylococcus aureus, Bacillus subtilis and Bacillus cereus.63

The investigation of the biosynthesis of the prenylflavonoids in C. tricuspidata has been attempted. Dai et al. 64 established a cell suspension culture of C. tricuspidata for the enzymatic preparation of prenylflavonoids. A flavonoid prenyltransferase was identified as C. tricuspidata isoliquiritigenin 3'-dimethylallyltransferase.64 This enzyme was found to be able to regioselectively introduce dimethylallyl diphosphate at the orthoposition of the phenolic moiety in the common 2,4-dihydroxyacetophenone substructure shared by the three types of flavonoids, i.e., chalcones, isoflavones, and flavones. 64,65 These studies could improve our knowledge of the mechanism of the biosynthesis and accumulation of prenylated flavonoids in C. tricuspidata.

The constituents and quantities of the flavonoids in C. tricuspidata fruits have been demonstrated to change in accordance with their maturation stage. Unripe fruits of C. tricuspidata were found to have a higher content of total flavonoids in comparison with ripe fruits. An analysis of the chemical constituents revealed that flavonoids with a side chain of cyclized prenyl 2,2-dimethylpyran rings were predominant in the unripe fruits, whereas flavonoids with a linear prenyl side chain were the main constituents in ripe fruits.66

Only a few studies have been reported concerning the quantitative analysis of representative flavonoids in C. tricuspidata. By UV-vis spectrophotometry, the concentration of total flavonoid glycosides in C. tricuspidata roots was measured to be up to 3.96 mg g⁻¹ (as rutin equivalents).⁶⁷ By HPLC analysis, the flavonoids kaempferol (118), quercetin (125), naringenin (146) and taxifolin (166) in C. tricuspidata were found to occur at 0.30, 0.09, 1.94 and 0.63 mg g^{-1} in the roots and 0.08, 0.04, 0.90 and 0.62 mg g⁻¹ in the stems, respectively.⁶⁸ Jeon et al.⁶⁹ reported the isolation of prenylated isoflavonoids from an n-hexane extract of C. tricuspidata fruits using centrifugal partition chromatography and found that the main flavonoids 4'-O-methylalpinumisoflavone (242), 6,8-diprenylgenistein (252) and 6,8-diprenylorobol (254) amounted to 2.7%, 7.6% and 6.4%, respectively.

3.3. Organic acids (258–289)

To date, thirty-one organic acids and their esters have been isolated from C. tricuspidata. The stem extract was reported to contain *n*-hexanoic acid (278) in the greatest concentration (9.89 $\mu g g^{-1}$) followed by 2-acetylpyrrole (405, 1.86 $\mu g g^{-1}$), whereas the root extract was found to have *n*-hexanoic acid (13.13 μ g g⁻¹) in the greatest concentration followed by n-heptanoic acid (279, 2.05 $\mu g g^{-1}$). Jung et al. 70 reported that the levels of organic acids such as citric acid (261), malic acid (264), oxalic acid (265), succinic acid (270) and tartaric acid (273) in C. tricuspidata fruits varied with the maturation stage, and malic acid was the most abundant.

3.4. Polysaccharides (290-295)

The yield of total polysaccharides (CTPS) amounted to 1.0% in the roots of C. tricuspidata.71 Six polysaccharides with strong Table 1 Chemical constituents of *C. tricuspidata*

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No. Compound name(s) Tissue(s) Ref. Xanthones Cudratricusxanthone A Whole plant 49 2 Cudratricusxanthone B Roots 17 Cudratricusxanthone C Roots 17 4 Cudratricusxanthone D Roots 17 Cudratricusxanthone E Roots 17 Cudratricusxanthone F Roots 17 Cudratricusxanthone G 17 Roots Cudratricusxanthone H Roots 17 Cudratricusxanthone I 55 Roots 10 Cudratricusxanthone I Roots 50 Cudratricusxanthone K 11 Roots 50 12 Cudratricusxanthone L Roots 50 Cudratricusxanthone M 13 Roots 50 14 Cudratricusxanthone N Roots 143 Cudratricusxanthone O 15 Roots 143 16 Cudratricusxanthone P/cudracuspixanthone A Roots 116 and 143 17 Cudraxanthone A Root bark 144 18 Cudrayanthone B Root bark 144 19 Cudraxanthone C Root bark 144 20 Cudraxanthone D Root bark 4 21 Cudraxanthone E Root bark 146 22 Cudraxanthone F Root bark 146 23 Cudraxanthone G Root bark 146 24 Cudrayanthone H Root bark 147 25 Cudraxanthone I 147 Root bark 26 Cudraxanthone J Root bark 147 27 Cudraxanthone K Root bark 147 28 Cudraxanthone L Root bark 148 29 Cudraxanthone M Root bark 148 30 Cudraxanthone N Root bark 148 Cudraxanthone O 31 Root bark 148 Cudracuspixanthone B/cudratrixanthone B 27 and 116 32 Roots Cudracuspixanthone C Roots 33 116 34 Cudracuspixanthone D Roots 116 35 Cudracuspixanthone E Roots 88 Cudracuspixanthone F 36 Roots 88 Cudracuspixanthone G 37 Roots 88 38 Cudratrixanthone A Root bark 27 39 Cudratrixanthone C Root bark 27 40 Cudratrixanthone D Root bark 27 41 Cudratrixanthone E Root bark 2.7 42 Cudratrixanthone F Root bark 2.7 43 Cudratrixanthone G Root bark 2.7 44 Cudratrixanthone H Root bark 27 27 45 Cudratrixanthone I Root bark 46 Cudratrixanthone J Root bark 27 27 47 Cudratrixanthone K Root bark 27 48 Cudratrixanthone L Root bark 49 Cudratrixanthone M 27 Root bark 50 Cudratrixanthone N Root bark 27 Cudratrixanthone O 27 51 Root bark 52 Cudratrixanthone P Root bark 145 53 Cudratrixanthone Q Root bark 145 54 Cudratrixanthone R Root bark 145 Cudratrixanthone S Root bark 145 55 56 Cudratrixanthone T Root bark 145 Cudratrixanthone U 57 Root bark 145 58 Cudratrixanthone V Root bark 145 59 Cudratrixanthone W Root bark 145 60 Alvaxanthone Roots 88 Alloathyriol 61 Roots 88 62 Dulxanthone B Twigs 75

Table 1 (Contd.)

No.	Compound name(s)	Tissue(s)	Ref.
53	Gerontoxanthone A	Root bark	25
54	Gerontoxanthone C	Root bark	27
55	Gerontoxanthone I	Roots	88
6	Isocudraniaxanthone A	Roots	116
57	Isocudraniaxanthone B	Root bark	56
8	Isocudraxanthone K	Root bark	25
9	Isogentisin	Roots	88
0	Isoalvaxanthone	Roots	88
1	Laxanthone I	Root bark	116
2	Macluraxanthone B	Whole plant	49
3	Macluraxanthone C	Roots	55
4	Nigrolineaxanthone F	Root bark	27
5	Neriifolone A	Root bark	27
6	Toxyloxanthone B	Root bark	145
7	Toxyloxanthone C	Roots	17
8	Xanthone V _{1a}	Roots	17
9	1-Trihydroxy-3,6,7-trimethoxyxanthone	Roots	55
0	1,3,5-Trihydroxy-4-prenylxanthone	Roots	116
1	1,3,5-Trihydroxy-2-(3-methylbut-2-enyl)xanthone	Root bark	27
2	1,3,5,6-Tetrahydroxyxanthone	Bark	149
3	1,3,6,7-Tetrahydroxy-2-(3-methylbut-2-enyl)-	Roots	52
	8-(2-methylbut-3-en-2-yl)-9 <i>H</i> -xanthen-9-one		
4	1,3,7-Trihydroxy-4-(1,1-dimethyl-2-propenyl)-	Roots	52
-	5,6-(2,2-dimethylchromeno)xanthone	110015	02
5	1,5-Dihydroxy-3,6-dimethoxyxanthen-9-one	Twigs	75
6	1,7-Dihydroxy-3,6-dimethoxyxanthone	Roots	55
7	1,6,7-Trihydroxy-2-(1,1-dimethyl-2-propenyl)-	Roots	119
,	3-methoxyxanthone	Roots	117
88	1,6,7-Trihydroxy-3-methyl-4-(1,1,3-trimethyl-2-	Root bark	23
00	buten-1-yl)-9 <i>H</i> -xanthen-9-one	ROOT DAIR	23
19		Root bark	116
	2-Deprenylrheediaxanthone B		116
0	2,6-Dihydroxyxanthone	Roots	116
1	3- <i>O</i> -Methylcudratrixanthone G	Root bark	27
2	5-O-Methylformoxanthone C	Root bark	27
3	6-Deoxyisojacareubin	Root bark	27
4	6-Deoxy-γ-mangostin	Root bark	27
5	7- <i>O</i> -Demethylcudratrixanthone C	Root bark	145
6	8-Prenylxanthone	Roots	88
7	16-Hydroxycudratrixanthone Q	Root bark	145
8	16-Hydroxycudratrixanthone M	Root bark	145
9	16-Methoxycudratrixanthone M	Root bark	145
lavonoids			
lavones			
.00	Artocarpesin	Roots and stems	17
01	Apigenin	Fruits	168
02	Apigenin-7- <i>O</i> -β- _D -glucopyranoside	Fruits	168
03	Cudraflavone A	Root bark	150
04	Cudraflavone B	Root bark	150
05	Cudraflavone C	Root bark	151
06	Cudraflavone D	Root bark	151
07	Cudraflavone F	Roots	58
08	Cudraflavone G	Roots	58
09	Cudraflavone H	Root bark	145
10	Cycloartocarpesin B	Roots	17
11	Cyclomorusin	Twigs	75
12	Cycloartocarpin	Whole plant	152
13	Hirsutrin/quercetin-3- <i>O</i> -β-D-glucopyranoside	Fruits	66
14	Kuwanon C	Roots	125
15	Licoflavone C	Leaves	153
	2.00114101100	Leaves	133
	5.7.2/4/-Tetrahydroxyflayone/norarthocarnetin	Stems	154
116 117	5,7,2′,4′-Tetrahydroxyflavone/norarthocarpetin 6-Prenylapigenin	Stems Roots	154 58

Table 1 (Contd.)

No.	Compound name(s)	Tissue(s)	Ref.
119	Kaempferol-3- <i>O</i> -β- _D -glucopyranoside/astragalin	Fruits	168
120	Kaempferol-7- <i>O</i> -β-D-glucopyranoside/populnin	Whole plant	155
121	6- <i>p</i> -Hydroxybenzyl kaempferol-7- <i>O</i> -β-D-glucopyranoside	Root bark	156
122	Morin	Root bark	124
123	Myricetin	Roots	117
124	Nicotiflorine	Fruits	168
125	Quercetin	Twigs, root bark and stems	75, 106 and 157
126	Quercetin-7- <i>O</i> -β-D-glucopyranoside/quercimeritrin	Root bark	158
127	6- <i>p</i> -Hydroxybenzyl quercetin-7- <i>O</i> -β-D-glucopyranoside	Root bark	156
128	Rutin	Fruits	66
Flavanones			
129	Cudraflavanone A	Root bark	158
130	Cudraflavanone B	Roots	125
131	Cudraflavanone C	Roots	55
32	Cudraflavanone D	Roots	55
133	Cudraflavanone E	Roots	58
134	Cudraflavanone F	Roots	58
135	Cudraflavanone G	Roots Root bark	145
.36	(2R)-Cudraflavanone H	Root bark	145
	(2S)-Cudraflavanone H	Root bark	145
137 138			75
	Cycloaltilisin 7	Twigs	
139	Cudracuspiflavanone A	Root bark	124
140	Carthamidin	Leaves	153
141	Dalenin	Root bark	145
142	Dicycloeuchrestaflavanone B	Root bark	145
143	Euchrestaflavanone B	Root bark	157
44	Euchrestaflavanone C	Root bark	157
145	Eriodictyol	Stem bark	30
146	Naringenin	Twigs and root bark	75 and 157
147	Pinocembrin	Root bark	145
148	Prunin	Fruits	168
149	Steppogenin	Twigs, roots and stems	75, 159 and 160
150	Tomentosanol D	Root barks	145
51	(2 <i>S</i>)-2′,5,7-Trihydroxy-6-(3-hydroxy-3-methylbutyl)-6″,6″-dimethylpyrano[2″,3″:4′,5′]flavanone	Roots	58
152	2′,5,7-Trihydroxy-4′,5′-(2,2-dimethylchromeno)-8- (3-hydroxy-3-methylbutyl)flavanone	Root bark	157
153	4'-Hydroxyisolonchocarpin	Root bark	145
154	5-Dehydroxybavachinone A	Root bark	145
155	5,7,3',5'-Tetrahydroxyflavanone	Root bark	124
156	6-Prenylnaringenin	Roots	161
157	8-Prenylnaringenin	Root bark	124
58	Aromadendrin/dihydrokaempferol	Root bark and twigs	75 and 156
159	Dihydrokaempferol-7- <i>O</i> -β-D-glucoside	Twigs	75 and 150
160	trans-Dihydromorin	Twigs and whole plant	133 and 152
161	Gericudranin A	Stem bark	16 and 132
162	Gericudranin B	Stem bark	16
163	Gericudranin C	Stem bark	16
164	Gericudranin D	Stem bark	58
165	Gericudranin E	Stem bark	58
166	Taxifolin/dihydroquercetin	Twigs and stems	75 and 160
167	Taxifolin-7-methyl ether	Twigs	75
168	Taxifolin-7- <i>O</i> -β-D-glucopyranoside	Twigs	75
169	Tricusposide	Bark	149
170	(2S,3S)-2,3-trans-Dihydromorin-7-O-β-D-glucoside	Twigs	75
171	(2 <i>R</i> ,3 <i>R</i>)-2,3-Dihydro-3,5,6,7-tetrahydroxy-2- (4-hydroxyphenyl)-4 <i>H</i> -1-benzopyran-4-one	Root bark	124
172	3,5,7,2',4'-Pentahydroxydihydroflavonol	Whole plant	152
.73	5,7,4'-Trihydroxy-8- <i>p</i> -hydroxybenzyldihydroflavonol	Root bark	124
soflavones	,,		
174	Cudraisoflavone B	Fruits	28
175	Cudraisoflavone C	Fruits	28
176	Cudraisoflavone D	Fruits	28
	Guaranounavone D	114165	20

Table 1 (Contd.)

No.	Compound name(s)	Tissue(s)	Ref.
177	Cudraisoflavone E	Fruits	28
178	Cudraisoflavone F	Fruits	28
179	Cudraisoflavone G	Fruits	28
180	Cudraisoflavone H	Fruits	28
181	Cudraisoflavone I	Fruits	28
182	Cudraisoflavone J Cudraisoflavone K	Fruits Fruits	28 28
183 184	Cudraisoflavone L (1)	Leaves	28 87
185	Cudraisoflavone L (1) Cudraisoflavone L (2)	Fruits	168
186	Cudraisoflavone L (2) Cudraisoflavone M	Fruits	168
187	Cudraisoflavone N	Fruits	168
188	Cudraisoflavone O	Fruits	168
189	Cudraisoflavone P	Fruits	168
190	Cudraisoflavone Q	Fruits	168
191	Cudraisoflavone R	Fruits	168
192	Cudraisoflavone S	Fruits	168
193	Cudraisoflavone T	Fruits	168
194	Cudracusisoflavone A	Fruits	66
195	Cudracusisoflavone B	Fruits	66
196	Auriculasin	Fruits	28
197	Anagyroidisoflavone A	Fruits	28
198	Alpinumisoflavone	Fruits	32
199	Biochanin A	Root bark	124
200	Erysenegalensein E	Fruits	31
201	Isoerysenegalensein E	Fruits	31
202	Erythrinin B/wighteone/6-isopentenylgenistein	Twigs and fruits	28 and 102
203	Erythrinin C	Fruits	28
204	Eryvarin B	Fruits	28
205	Erysubin A	Leaves	87
206	Euchrenone b8	Fruits	28
207	Euchrenone b9	Fruits	28
208	Euchrenone b10	Fruits	28
209	Erythrivarone A	Leaves	153
210	Derrone	Fruits	28
211	Derrone-4'-O-methyl ether	Fruits	66
212	Flaniostatin	Leaves	162
213	Flemiphilippinin B	Whole plants	163
214	Flemiphilippinin G	Fruits	28
215	Furowanin B	Leaves	86
216	Gancaonin A	Fruits	116
217	Gancaonin B	Fruits	28
218	Genistein	Twigs and bark	75 and 149
219	Genistein-4'-O-β-glucopyranoside/sophorobioside	Fruits	168
220	Genistin	Bark	149
221	Glycyrrhisoflavone	Twigs	75 06
222	Isolupalbigenin Isochandalone	Leaves	86
223 224	Lupiwighteone	Fruits	66
	Lupiwighteone Lupalbigenin	Fruits Leaves	28 87
225 226	Lupaibigenin Laburnetin	Root bark	87 145
226 227	Millewanin H	Leaves	87
227 228	Millewanin G	Leaves	153
228 229	Osajin	Fruits	32
230	Orobol	Fruits	31
230 231	Oroboside	Fruits	66
232	Orobol-8-C-glucoside	Twigs	75
233	Pomiferin	Fruits	32
233 234	Parvisoflavone A	Root bark	145
234 235	Senegalensin	Fruits	31
236	Santal	Twigs	75
237	Sphaerobioside	Twigs	75 75
238	Ulexin B	Fruits	66
	Ulexone B	Fruits	00

Table 1 (Contd.)

No.	Compound name(s)	Tissue(s)	Ref.
240	Warangalon	Fruits	28
241	3'-O-Methylorobol	Root bark	124
42	4'-O-Methylalpinumisoflavone	Fruits and stem bark	105 and 11
43	4'-O-Methylcudraisoflavone O	Fruits	168
44	4'-O-Methylcudraisoflavone P	Fruits	168
45	4'-O-Methylerythrinin C	Fruits	168
46	4',7-Dihydroxy-5-methoxyisoflavone/5- <i>O</i> -methylgenistein	Stems	154
247	5,3'-Dihydroxy-4'-methoxy-2",2"-	Fruits	31
	dimethylpyrano[5",6";6,7]isoflavone		
248	5,3',4'-Trihydroxy-6",6"-	Fruits	66
	dimethylpyrano[2",3";7,6]isoflavone	_	
249	5,4'-Dihydroxy-8-(3"-methylbut-2"-enyl)-	Fruits	31
	2'''-(4'''-hydroxy-4'''-methylethyl)furano[4''',5''';6,7]isoflavone		
250	5,4'-Dihydroxy-6-(3"-methylbut-2"-enyl)-	Fruits	31
	2'''-(4'''-hydroxy-4'''-methylethyl)-3'''-		
	methoxydihydrofurano[4"',5"';7,8]isoflavone		
51	5,7-Dihydroxy-6-(2"-hydroxy-3"-	Fruits	31
	methylbut-3"-enyl)-4'-methoxyisoflavone		
52	5,7,4'-Trihydroxy-6,8-diprenylisoflavone/	Fruits	32 and 75
152	6,8-diprenylgenistein/8- $(\gamma, \gamma$ -dimethylallyl)wighteone	Trutts	32 and 73
152	5,7,4'-Trihydroxydihydroisoflavone	Whole plant	152
253		Whole plant	
254	6,8-Diprenylorobol/5,7,3',4'-tetrahydroxy-6,8-diprenylisoflavone	Twigs and fruits	28 and 75
255	6-Prenylorobol	Leaves	153
256	7,4'-Dimethoxy-5-hydroxyisoflavone	Fruits	66
257	8-Hydroxygenistein	Root bark	145
Organic a	cids		
258	Butyl citrate	Trunk	15
259	Benzoic acid	Fruits	76
260	Boric acid	Fruits	76 76
261	Citric acid	Fruits	70
262	Mandelic acid	Fruits	76
263	Methyl linoleate	Trunk	15
264	Malic acid	Fruits	70
265	Oxalic acid	Fruits	70
266	Palmitic acid	Trunk	15
267	Palmitic acid methyl ester	Trunk	15
268	Palmitic acid β-monoglyceride	Trunk	15
269	Protocatechuic acid	Twigs	75
270	Succinic acid	Fruits	70
271	Stearic acid	Trunk	15
272	Syringic acid	Trunk	15
73	Tartaric acid	Fruits	70
274	threo-9,10-O-Isopropylidene-13-hydroxy-(11E)-octadecenoic acid	Roots	164
275	n-Decanoic acid	Roots and stems	10
276	n-Nonanoic acid	Roots	10
277	n-Pentanoic acid	Roots and stems	10
278	n-Hexanoic acid	Roots and stems	10
79	n-Heptanoic acid	Roots	10
80	n-Octanoic acid	Roots	10
81	(E)-2-Decenoic acid	Roots	10
82	(E)-2-Octenoic acid	Roots and stems	10
83	2',3'-Dihydroxypropyl pentadecanoate	Roots	165
84	4-Hydroxybenzoic acid	Fruits	168
85	9,12-Octadecadienoic acid	Trunk	15
86	9,12,15-Octadecatrienoic acid methyl ester	Trunk	15
87	9,12,15-Octadecatrien-1-ol	Trunk	15
88	9,17-Octadecadienal	Trunk	15
289	γ-Hexadecalactone	Root bark	145
olysacch	arides		
oiysaccii 90	CTP-B1	Roots	73
		Roots	72

Table 1 (Contd.)

No.	Compound name(s)	Tissue(s)	Ref.
292	CPS-0	Roots	71
293	CTPS-1A	Roots	71
94	CTPS-2B	Roots	71
295	CTPS-3A	Roots	71
henylpro	ppanoids		
96	Bergapten	Root bark	145
97	Cudrastilbene	Roots	159
98	cis-3',4'-Diisovalerylkhellactone	Root bark	145
99	Demethylsuberosin	Whole plant	163
00	Decursinol angelate	Root bark	145
01	Gomisin A	Roots	166
02	Gomisin H	Roots	166
03	Hyuganin C	Root bark	145
04 05	Imperatorin	Whole plant	163 163
	Isoimperatorin	Whole plant	75
06 07	Oxyresveratrol Scopoletin	Twigs Trunk	75 15
07 08	Schizandrin	Whole plant	15 166
08 09	Syringaresinol	Whole plant	166
10	Umbelliferone	Root bark	151
11	Xanthyletin	Root bark	145
12	7-Hydroxy-2 <i>H</i> -1-benzopyran-2-one	Trunk	15
13	5-Methoxy-4,5-diphenyl-2(5 <i>H</i>)-furanone	Twigs	75
14	3-Methyl- $2(5H)$ -furanone	Roots	10
15	5-Ethyl-2(5 <i>H</i>)-furanone	Roots	10
16	5,5-Dimethyl-2(5 <i>H</i>)-furanone	Roots	10
Other ing	redients		
17	Betulin	Roots	165
18	Butyrospermol	Fruits	168
19	Camphene	Roots	10
20	Drimenol	Roots	10
21	Dihydroctinidiolide	Stems	10
22	Glutinol	Root bark	145
23	Lupeol	Roots	165
24	Lanosta-8-24-dien-3β-ol-acetate	Trunk	15
25	Lanosta-8-en-3-one	Trunk	15
26	Lanosta-7,24-diene-3β-ol Lanosta-7,24-diene-3β <i>-O</i> -acetate	Whole plant	152
27	Olean-12-ene	Whole plant	152
28 29	Taraxerone	Trunk Stems	15 160
29 30	Terpin hydrate	Roots	10
30 31	Ursolic acid	Roots	165
32	(E)-Geranylacetone	Roots	103
33	(E) - β -Ionone	Roots and stems	10
34	(E)-Linalool oxide	Roots	10
35	(Z)-Linalool oxide	Roots	10
36	(E)-α-Terpineol	Roots and stems	10
37	α-Amyrin	Root bark	145
38	Campesterol	Trunk	15
39	Daucosterol	Roots	165
40	Itesmol	Roots	165
41	β-Sitosterol	Roots	165
42	γ-Sitosterol	Trunk	15
43	Achilleol A	Whole plant	163
44	Antiarol	Fruits	76
45	Anisaldehyde	Roots	10
46	Aristolone	Trunk	15
47	Adacene 12	Fruits	76
48	Brosimine B	Root bark	145
49	Benzophenone	Stems	10
550	Benzylhydrazine	Fruits	76

Table 1 (Contd.)

No.	Compound name(s)	Tissue(s)	Ref.
351	Bis(2-azabicyclo[2.2.1]hept-5-en-2-yl)diazene	Fruits	76
352	Butylated hydroxytoluene	Fruits	76
553	Cudracuspiphenone A	Roots	116
354	Cudracuspiphenone B	Roots	116
355	Cudrachromone A	Root bark	145
356	Cudraphenol A	Root bark	145
357	Cudraphenol B	Root bark	145
358	Cudraphenol C	Root bark	145
359	Cudraphenone E	Root bark	145
360	Cudradihydrochalcone A	Fruits	168
361	Cudrabibenzyl A	Fruits	168
362	(E)-Cinnamic aldehyde	Roots and stems	10
363	Dopamine	Fruits	76
364	Demeton-O-methyl	Fruits	76
365	Diethyl phthalate	Fruits	76
366	Ethyl- <i>N</i> -methylcarbamate	Fruits	76
367	Eriosematin A	Root bark	145
368	Ethyl <i>p-tert</i> -butylbenzoic acid	Fruits	76
369	Eugenol	Roots and stems	10
370	Isoeugenol	Roots	10
371	Isoencecalin	Root bark	145
372	Indene	Fruits	76
373	Lavender lactone	Roots	10
374	Lycopene	Fruits	77
375	Lutein	Fruits	77
376	Palustrol	Fruits	76
377	Peonoside	Bark	149
378	Phenol	Fruits, roots and stems	10 and 76
379	Phytofluene	Fruits	77
380	Phenylethyl alcohol	Roots and stems	10
381	Pyridine	Roots	10
382	Pyrrole-2-carboxaldehyde	Stems	10
383	Ruboxanthin	Fruits	77
	Salicylamide	Fruits	77 76
384		Fruits	76 76
385	Scyllitol Sucrose	Bark	149
386			
387	Stachydrine	Roots	167
388	Tridecanol	Fruits	76 76
389	Undecane	Fruits	76
390	Vanillin	Root bark	145
391	Zeaxanthin	Fruits	77
392	p-Vinylguaiacol	Roots and stems	10
393	n-Hexanal	Roots	10
394	n-Hexanol	Roots	10
395	n-Butanol	Roots	10
396	n-Nonanal	Roots and stems	10
397	N-Acetylnorephedrine	Fruits	76 - 6
398	1-Phenyl-1-cyclohexylethane	Fruits	76
399	1-Methyl-2-pyrrolidone	Roots and stems	10
100	1-[(2,4,6-Trimethylphenyl)methyl]imidazole	Fruits	76
101	(4S)-1,1-Difluoro-4 vinylspiropentane	Fruits	76
102	2-Deuteriophenylalanine	Fruits	76
103	2-Furanmethanol	Trunk	15
104	2-Ethyl-1-hexanol	Roots and stems	10
105	2-Acetylpyrrole	Stems	10
106	2,3-Dihydro-3,5-dihydroxy-6-methyl-4 <i>H</i> -pyran-4-one	Trunk	15
407	2,4-Bis(4-hydroxybenzyl)phenol	Root bark and stems	10 and 14
108	2,5-Furandione	Trunk	15
109	3-Methoxycarbonylindole	Root bark	145
410	3-Methyl-2,5-furandione	Trunk	15
111	4-Acetylpyrazole	Roots	10
	4-Ethylguaiacol	Roots and stems	10
412	4-Euryiguaiacoi		

Table 1 (Contd.)

No.	Compound name(s)	Tissue(s)	Ref.
414	4-Hydroxymethylbenzoate	Root bark	145
415	4-(Methoxymethyl)phenol	Whole plant	163
416	4-Methyltridecane	Fruits	76
417	4-Methylguaiacol	Roots	10
418	4-Hydroxybenzaldehyde/p-hydroxybenzaldehyde	Trunk	15
429	4-Valerolactone	Roots and stems	10
420	4,4-Diphenyl-5-methyl-2-cyclohexenone	Fruits	76
421	<i>p</i> -Hydroxybenzyl alcohol	Trunk	15
422	5-(Hydroxymethyl)-2-furancarboxaldehyde	Trunk	15
423	5-Hydroxy-2,2-dimethyl-2 <i>H</i> ,6 <i>H</i> -benzodipyran-6-one	Root bark	124
424	5-Methyl-1 <i>H</i> -pyrrole-2-carboxaldehyde	Stems	10
425	5,7-Dihydroxychromone	Root bark	124
426	6-Pentyl-5,6-dihydro-2 <i>H</i> -pyran-2-one	Roots and stems	10
427	8-Chloro-6-(2-fluorophenyl)imidazole[1,2-a][1,4]benzodiazepine	Fruits	76
428	α-Carotene	Fruits	77
429	β-Carotene	Fruits	77
430	Neo-β-carotene	Fruits	77
431	γ-Amylbutyrolactone	Roots and stems	10
432	γ-Butylbutyrolactone	Roots and stems	10
433	γ-Butyrolactone	Roots	10
434	γ-Caprolactone	Roots	10
435	γ-Crotonolactone	Roots	10
436	γ-Dodecalactone	Roots and stems	10
437	γ-Palmitolactone	Roots	10
438	Arginine	Roots	167
439	Alanine	Roots	167
440	Aspartate	Roots	167
441	Glutamic acid	Roots	167
442	Proline	Roots	167
443	Polycopene	Fruits	77

immunomodulatory activities, namely, CTP-B1 (290), CTPS-01 (291), CPS-0 (292), CTPS-1A (293), CTPS-2B (294) and CTPS-3A (295), were obtained from the roots of *C. tricuspidata*. Their backbones were revealed to be commonly substituted with α -D-glucuronic acid, 4-O-methyl- α -D-glucuronic acid, and neutral sugar units such as α -L-arabinose, α -D-xylose and α -D-galactose. A

3.5. Phenylpropanoids (296–316)

Twenty-one phenylpropanoids have been reported in *C. tricus-pidata*, such as oxyresveratrol (306),⁷⁵ scopoletin (307),¹⁵ 3-methyl-2(5*H*)-furanone (314),¹⁰ and 5-ethyl-2(5*H*)-furanone (315).¹⁰ Oxyresveratrol, as a representative phenylpropanoid, was isolated from the twigs of *C. tricuspidata*, exhibited potent inhibitory activity against mushroom tyrosinase and might serve as an anti-browning agent for food.⁷⁵

3.6. Others (317-443)

In addition to the aforementioned components, a large number of other components have also been identified in *C. tricuspidata*. Twenty-nine compounds were identified in the essential oil of *C. tricuspidata* fruits, which accounted for 94.46% of the essential oil, such as demeton-*O*-methyl (364), diethyl phthalate (365), ethyl-*N*-methylcarbamate (366), indene (372), scyllitol

(385), tridecanol (388) and 1-phenyl-1-cyclohexylethane (398).⁷⁶ It should be mentioned that a series of carotenoids were identified in *C. tricuspidata* fruits, including lycopene (374), lutein (375), phytofluene (379), ruboxanthin (383), zeaxanthin (391), α -carotene (428), β -carotene (429), neo- β -carotene (430) and polycopene (443).⁷⁷

4 Pharmacological properties

Accumulated studies have revealed that the extracts and components of *C. tricuspidata* exhibited a broad spectrum of pharmacological activities, including anti-inflammatory,^{22,23} antioxidant,^{78,79} antitumor,^{16,24} hepatoprotective,^{25,26} neuroprotective,^{27,28} antiobesity,^{18,19} immunomodulatory,^{70,71} anti-atherosclerotic,^{80,81} antimicrobial,^{11,76} skin-protecting,^{79,82} and antidiabetic^{21,52} effects. The presence of a variety of bioactive compounds may be synergistically or individually responsible for the various activities of this species (Fig. 3). Among these, xanthones and flavonoids are representative ingredients that mainly possess anti-inflammatory, antioxidant and antitumor activities.

4.1. Anti-inflammatory activity

There has been strong evidence that diseases associated with inflammation may be ameliorated by *C. tricuspidata*. The anti-

Xanthones **47** R = CH₂OH **50** R = Me 53 98 R = OH 99 R = OMe

Fig. 2 Chemical structures of xanthones and flavonoids isolated from C. tricuspidata.

inflammatory molecular mechanisms could be elucidated on the basis of the effects of the extracts and compounds from C. tricuspidata (Fig. 4). It has been reported that a methanolic extract of C. tricuspidata could decrease the production of the pro-inflammatory cytokines interleukin-2 (IL-2) and interferon- γ (IFN- γ) by selectively inhibiting the proliferation of anti-CD3/CD28-mediated CD4 $^{+}$ CD25 $^{-}$ T-cells. 15 The chloroform (CHCl $_{3}$)

fraction of *C. tricuspidata* was observed to inhibit the over-production of nitric oxide (NO) and prostaglandin E_2 (PGE₂) by decreasing the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) and reducing the levels of tumor necrosis factor- α (TNF- α), IL-1 β and IL-6 in RAW 264.7 mouse macrophage cells stimulated with lipopolysaccharide (LPS).⁸³ The ethyl acetate (EtOAc) fraction of the stem bark could

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Flavonoids 103 $\begin{array}{l} {\rm A,\,R_2=R_3=H,\,R_4=OH} \\ {\rm R_3=A,\,R_2=OH,\,R_4=H} \\ {\rm R_2=R_3=H,\,R_4=OH} \end{array}$ 109 $\begin{aligned} &R_2 = R_4 = OH, \, R_3 = H \\ &R_2 = R_4 = OH, \, R_3 = H \\ &R_2 = R_4 = OH, \, R_3 = A \\ &4 = H, \, R_2 = OH, \, R_3 = C \\ &R_2 = R_4 = OH, \, R_3 = H \end{aligned}$ 111 112 138 153

Fig. 2 (contd.)

suppress the production of NO and expression of iNOS in RAW 264.7 cells stimulated with IFN- γ /LPS *via* the inactivation of nuclear factor- κ B (NF- κ B). ⁸⁴ The EtOAc fraction of *C. tricuspidata* stem bark could inhibit the differentiation of osteoclasts stimulated by IL-1 β and mediated by receptor activator of NF- κ B ligand, the phosphorylation of extracellular signal-regulated kinase (ERK) 1/2 and p38 mitogen-activated protein kinase (MAPK), and the expression of c-Fos and nuclear factor of activated T-cells c1 (NFATc1). ⁸⁵ The EtOAc fraction of the whole plant was also found to reduce the expression of IL-1 β , matrix metalloproteinases (MMPs), COX-2 and PGE₂ by inhibiting the phosphorylation of MAPK and the activation of NF- κ B signalling pathways in rheumatoid synovial fibroblasts. ⁸⁶ The above research suggested that *C. tricuspidata* may be useful for

managing bone destruction in inflammatory diseases, such as rheumatoid arthritis (RA).

Numerous compounds from *C. tricuspidata* possess noticeable anti-inflammatory properties. Prenylated isoflavones from the leaves of *C. tricuspidata*, including cudraisoflavone L (184), wighteone (202) and furowanin B (215) exhibited potential anti-inflammatory activity by inhibiting the production of NO in LPS-stimulated RAW 264.7 cells, with inhibition values of 72.5 \pm 2.4%, 66.9 \pm 1.8%, and 55.4 \pm 2.7% at a concentration of 10 μ M, respectively.⁸⁷ It was found that the position of hydroxyl groups in the xanthone moiety was important for the NO-inhibiting activity, and the catechol moiety was partially responsible for the inhibitory activity (Table 2).⁸⁸ A *C. tricuspidata* glycoprotein suppressed the expression of iNOS and COX-2

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Fig. 2 (contd.)

via the regulation of NF-κB in LPS-stimulated RAW 264.7 cells.³⁴ The xanthone CTXA, as an effective inducer of heme oxygenase-1 (HO-1), significantly inhibited the production of PGE₂, NO, TNF- α , and IL-1 β and increased the activity of HO in LPSstimulated RAW 264.7 macrophages.²² Moreover, CTXA could exert anti-soluble endothelial cell protein C receptor (antisEPCR) shedding activity against vascular inflammation via inhibiting the expression of TNF- α -converting enzyme induced by phorbol-12-myristate-13-acetate in endothelial cells.89 Cudraflavone B was not only a potent inhibitor of TNF-α by blocking the translocation of NF-κB from the cytoplasm to the nucleus in macrophages derived from a THP-1 human monocytic leukemia cell line, but was also an inhibitor of COX-1 and COX-2 with higher selectivity toward COX-2, which suggested that it could be used as a lead for the development of nonsteroidal anti-inflammatory drugs.60

Allergic inflammation affects roughly one-quarter of people in the world. 90 5,7,3′,4′-Tetrahydroxy-6,8-diprenylisoflavone (254) not only interfered with the interaction between IgE and high-affinity IgE receptor (FceRI) and the expression of FceRIß mRNA but also inhibited the redistribution of F-actin and downstream signalling by suppressing the activation of FceRI-mediated spleen tyrosine kinase in mast cells, which was suggestive of therapeutic potential for controlling mast cell activation in allergic processes. Treatment with the *C. tricus-pidata* glycoprotein resulted in degranulation for allergic response (β -hexosaminidase) and the activation of MAPK/activator protein-1 (AP-1) and NF- κ B, as well as the expression of cytokines related to allergic inflammation (IL-4, IL-6, TNF- α , IFN- γ , and IL-1 β), which are indirectly activated by bisphenol A or di(2-ethylhexyl) phthalate in HMC-1 and RBL-2H3 cells. $^{33,92-96}$

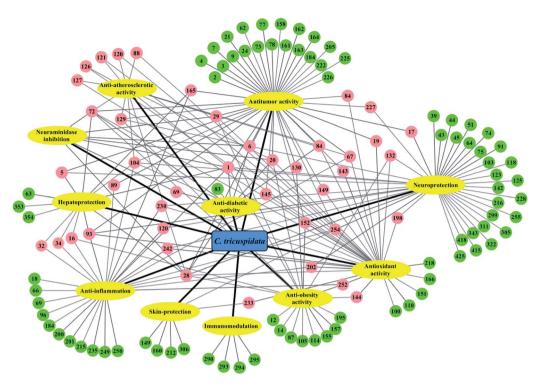


Fig. 3 Pharmacological activities of 124 active components from C. tricuspidata. The active compounds (circles) map ten pharmacological properties (yellow ovals). The pink circles represent multiple pharmacological properties. The green circles represent only one pharmacological property.

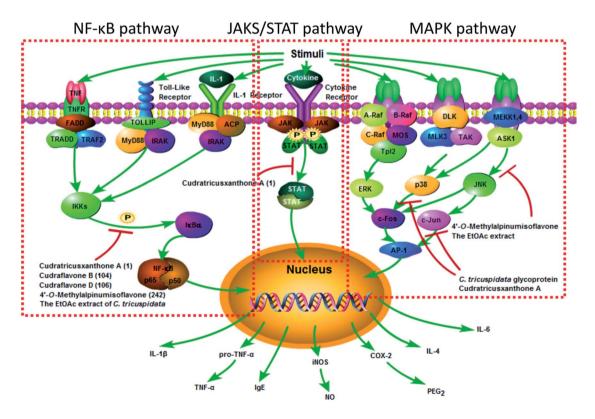


Fig. 4 Molecular mechanisms of anti-inflammatory extracts and compounds from C. tricuspidata.

Table 2 Anti-inflammatory activities of prenylated xanthones and flavonoids against LPS-induced RAW 264.7 cells

Compd	$IC_{50}\left(\mu M\right)$	Ref.	Compd	$IC_{50}\left(\mu M\right)$	Ref.
16	21.4	88	96	19.8	88
18	20.1	88	200	18.4	31
28	17.8	88	201	12.7	31
32	20.0	88	230	18.7	31
34	23.5	88	235	13.1	31
66	18.0	88	249	12.1	31
67	24.8	88	250	11.8	31
69	18.7	88	252	19.2	31
89	16.1	88			

4.2. Antioxidant activity

Evidence has mounted that *C. tricuspidata* could act as an efficient free-radical scavenger and thus help the antioxidant defense system (Table 3). *C. tricuspidata* leaves, in comparison with other parts, exhibited the highest scavenging activities against the 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radicals and the highest ferric reducing/antioxidant power (FRAP), which was correlated with their high level of polyphenols (73.60 \pm 0.28 mg g⁻¹), in particular quercetin.^{97,98} It has been reported that *C. tricuspidata* leaves could produce more quercetin and kaempferol aglycones *via Lactobacillus*-mediated fermentation,

which would increase antioxidant activities (DPPH and ABTS assays), and thereby could be developed as high-value-added food materials and functional foods.99-102 An aqueous extract of C. tricuspidata (2 mg mL⁻¹) exhibited significant scavenging activities of 50.2% (ABTS) and 40.5% (FRAP), respectively. 103 The antioxidant activity of C. tricuspidata fruits was revealed to change depending on the maturation stage and was positively associated with the contents of prenylflavonoids such as artocarpesin (100), alpinumisoflavone (198), 6-isopentenylgenistein (202), 4'-O-methylalpinumisoflavone and 6,8-diprenylgenistein. 104 The prenyl group on the A-ring of isoflavone was a potent contributor against the ABTS radical system. 105 The C. tricuspidata glycoprotein (100 μg mL⁻¹) exhibited strong scavenging activities against DPPH, superoxide anions and hydroxyl radicals, with no pro-oxidant activity in vitro.³⁴ It should be interesting to investigate the in vivo antioxidant potentials of these compounds for preventing various radical-mediated injuries in pathological situations.

4.3. Antitumor activity

During recent decades, *C. tricuspidata* has been demonstrated to possess promising antitumor and cytotoxic activities, and its cortices and root bark have been widely employed in TCM clinics for the treatment of cancer of the alimentary system, in particular gastric carcinoma.^{7,55} An EtOAc extract of

 Table 3
 Antioxidant activities of extracts and compounds of C. tricuspidata^a

	IC_{50}				
Sample	DPPH	ABTS	TBARS	Ref.	
The MeOH extract of leaves	13.29 μg m L^{-1}	N.A	N.A	78	
The MeOH extract of root bark	54.48 mg mL^{-1}	N.A	15.13 mg mL^{-1}	156	
The ethyl ether fraction of MeOH extract of root bark	30.78 mg mL^{-1}	N.A	7.72 mg mL^{-1}	156	
The EtOAc fraction of MeOH extract of root bark	20.32 mg mL^{-1}	N.A	7.46 mg mL^{-1}	156	
The <i>n</i> -BuOH fraction of MeOH extract of root bark	93.37 mg mL^{-1}	N.A	>20 mg mL ⁻¹	156	
Compd 20	N.A	N.A	6.2 μM	23	
Compd 28	N.A	N.A	3.8 μΜ	23	
Compd 29	N.A	N.A	2.2 μΜ	23	
Compd 67	N.A	N.A	0.8 μΜ	23	
Compd 72	N.A	N.A	4.5 μΜ	23	
Compd 84	N.A	N.A	12.6 μΜ	23	
Compd 88	N.A	N.A	2.6 μΜ	23	
Compd 104	>300 μM	4.2 μM	N.A	157	
Compd 110	>300 μM	8.2 μM	N.A	157	
Compd 120	$4.14~\mu\mathrm{g~mL}^{-1}$	N.A	$3.65~\mu g~mL^{-1}$	156	
Compd 121	$5.94 \ \mu g \ mL^{-1}$	N.A	$3.24~\mu {\rm g}~{\rm mL}^{-1}$	156	
Compd 126	$4.04~\mu\mathrm{g~mL}^{-1}$	N.A	$3.72~\mu\mathrm{g~mL}^{-1}$	156	
Compd 127	$5.50 \ \mu g \ mL^{-1}$	N.A	$3.71~\mu {\rm g}~{\rm mL}^{-1}$	156	
Compd 143	>300 µM	5.4 μM	N.A	157	
Compd 144	>300 μM	6.0 μ M	N.A	157	
Compd 145	N.A	N.A	$3~\mu g~mL^{-1}$	30	
Compd 149	N.A	N.A	$10~\mu\mathrm{g~mL}^{-1}$	30	
Compd 152	>300 μ M	8.3 μM	N.A	157	
Compd 166	N.A	N.A	$6~\mu g~mL^{-1}$	30	
Compd 230	N.A	N.A	$3 \mu \text{g mL}^{-1}$	30	
Compd 254	>200 μM	16.3 μΜ	N.A	105	

a N.A = not available.

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C. tricuspidata stem bark displayed significant cytotoxicity against HL-60 cells, and the mechanism underlying its cytotoxicity may be due to apoptosis. ¹⁰⁶ A CHCl₃ extract of *C. tricuspidata* roots exhibited significant cytotoxicity against human gastric carcinoma cell lines (SGC-7901 and BGC-823). ¹⁷ An MeOH extract of *C. tricuspidata* stems could induce the apoptosis of cervical cancer cells *via* the extrinsic pathway, as well as *via* the repression of human papillomavirus type-16 oncoproteins E6 and E7 and the alteration of p53 and p-pRb protein levels, instead of cytotoxicity. ¹⁰⁷ In nude mouse models of B16 melanoma and human SK-OV3 xenografted tumors, the tumor-inhibiting rates of the total flavonoids (250 mg kg⁻¹) from *C. tricuspidata* were 50.54% and 46.38%, respectively. ¹⁰⁸

Several compounds isolated from C. tricuspidata displayed considerable inhibitory activity against various tumor cells in an MTT assay (Table 4). The isoprenylated xanthones 20, 28, and 29 exhibited potent cytotoxic activity against HL-60 cells owing to apoptosis in a DNA fragmentation assay.⁵⁶ Gericudranins A-E isolated from the stem bark of C. tricuspidata exhibited cytotoxicity against human tumor cell lines such as CRL1579 (skin), LOX-IMVI (skin), MOLT-4F (leukemia), KM12 (colon) and UO-31 (renal).16,58 The p-hydroxybenzyl moiety at C-6 was revealed to be essential for the cytotoxic activity. 16,58 2',5,7-Trihydroxy-4',5'-(2,2-dimethylchromeno)-8-(3-hydroxy-3-methylbutyl)flavanone (152) could inhibit the activity of topoisomerase I ($IC_{50} = 1.0 \text{ mM}$) and induce apoptotic cell death of U937 human leukemia cells, at least in part, via the inhibition of DNA topoisomerase I activity. 109 Cudraflavanone A (129) inhibited mammalian topoisomerase I with an IC₅₀ of 0.4 mM and inhibited the activity of protein kinase C with an IC₅₀ of 150 μM.¹¹⁰ Euchrestaflavanone B could inhibit the activity of protein kinase CKII with an IC50 of 78 µM.111 Cudraflavone B was demonstrated to be a lead for the development of a potential candidate for treating human oral squamous cell carcinoma cells via the activation of MAPK and NF-κB, as well as the silent information regulator 1 (SIRT1) pathway.61 Cudraxanthone H (24) and isocudraxanthone K (62) exerted significant antiproliferative and apoptosisinducing effects in oral squamous cell carcinoma cells (IC50 values of 14.31 and 17.91 μM for HNSCC4 and 14.91 and 20.01 μM for HNSCC12 after treatment for 72 h) via the NF-κB and NIMA-interacting 1 pathways and mitochondrial death receptor, MAPK, NF-κB, and HIF-1α signalling pathways, respectively.112,113 Likewise, the cytotoxic effect of cudraflavone B was also documented against HNSCC4 cells (IC50 of 18.3, 12.6, and 10.9 µM after treatment for 24, 48, and 72 h) and HNSCC12 cells (IC50 of 19.5, 12.0, and 10.7 µM after treatment for 24, 48, and 72 h).61 CTXA could suppress the migration and invasion of MCF-7 and MDA-MB-231 breast cancer cells by downregulating MMP-9 and induce apoptosis by activating the mitochondrial-associated apoptotic signalling pathway, which suggests that it may be a novel antitumor agent for breast cancer therapy.114 Cudratricusxanthone G could inhibit the proliferation, migration and invasion of SW620 human colorectal carcinoma cells instead of displaying cytotoxicity by targeting MMP-2, thereby regulating the

activation of Rac1, Cdc42 and their downstream target AP-1.²⁴ Notably, the chemical and biogenic synthesis and molecular modification of unique compounds isolated from *C. tricuspidata* have attracted attention. For example, from gericudranin A a series of derivatives were synthesized by structural modification, some of which exhibited strong cytotoxicity against several cancer cell lines such as SNB19, MOLT-4F, and K562 cells in a sulforhodamine B assay.¹¹⁵ It is suggested that more attention should be paid to the SAR and *in vivo* antitumor mechanisms of the antitumor constituents of *C. tricuspidata*.

4.4. Hepatoprotective activity

Liver disease remains one of the most serious health problems without satisfactory drugs. The CHCl3 fraction of an MeOH extract of C. tricuspidata root bark exhibited a significant hepatoprotective effect on tacrine-induced cytotoxicity in HepG2 cells.26 CTXA, cudratricusxanthone E, cudraxanthone L and macluraxanthone B, which were isolated from the CHCl3 fraction, displayed the strongest hepatoprotective effects on tacrineinduced cytotoxicity in HepG2 cells at 10 µg mL⁻¹.26 Cudraflavone B and gericudranin E were further isolated from this MeOH extract and displayed significant protective effects against tacrine-induced cytotoxicity in HepG2 cells, with EC50 values of 37.39 and 39.87 μM, respectively.25 Cudracuspixanthone A (16) and cudracuspiphenones A (353) and B (354) exhibited moderate antiproliferative activity against HSC-T6 cells, with IC₅₀ values of 9.7, 3.3, and 7.1 μM, respectively. 116 It was demonstrated that 1,1-dimethylallyl or 2,3,3-trimethyl-2,3dihydrofuran moieties in the xanthones played important roles for the inhibitory activity. 116 The glycoprotein (75 kDa) isolated from C. tricuspidata fruits was effective in preventing CCl4-induced liver damage in A/J mice by significantly increasing the activities of superoxide dismutase, catalase, and glutathione peroxidase, as well as decreasing the production of TBARS, lactate dehydrogenase (LDH) and NO.35 These constituents might be preferred alternatives for liver disease, and in vivo assays are essential to ascertain their hepatoprotective role fully.

4.5. Neuroprotective activity

An aqueous extract of *C. tricuspidata* roots exhibited a stronger protective effect against neurotoxicity induced by oxidative stress than those of leaves, stems, and fruits, which was correlated with its high level of phenolic compounds, in particular kaempferol, myricetin (123) and quercetin.¹¹⁷ CTXA and cudraflavone B displayed significant neuroprotective activity against glutamate-induced neurotoxicity *via* the induction of HO-1 in HT22 mouse hippocampal cells.^{51,62} The neuroprotective effect of cudraflavone B was probably regulated by the phosphatidylinositol 3-kinase (PI3K)/AKT pathways.⁶²

MAOs are responsible for the degradation of neurotransmitters including noradrenaline, dopamine, and 5-hydroxy-tryptamine in the central nervous system. The dichloromethane (CH₂Cl₂) fraction of *C. tricuspidata* fruits was active in inhibiting mouse brain MAO, and gancaonin A (216),

Table 4 Cytotoxic activities of extracts, xanthones and flavonoids against tumor cells

Sample	Model	Active concentration	Ref.	Sample	Model	Active concentration	Ref
The EtOAc extract	HL-60 ^a	$30 \ \mu g \ mL^{-1} \left(IC_{50}\right)$	106	The EtOAc fraction	MCF-7	66.8 μg mL ⁻¹ (IC ₅₀)	142
of stem bark	$U937^b$	$40 \ \mu g \ mL^{-1} \left(IC_{50} \right)$	106	of fruits	$MDA-MB-231^f$	75.4 $\mu g \text{ mL}^{-1} (IC_{50})$	142
	$HeLa^c$	$58 \mu g \text{ mL}^{-1} (IC_{50})$	106	Total flavonoids	BGC-823 ^g	6.11 $\mu g \text{ mL}^{-1} (IC_{50})$	107
	$MCF-7^d$	$44 \mu g \text{ mL}^{-1} (IC_{50})$	106		$A549^h$	12.20 $\mu g \text{ mL}^{-1} (IC_{50})$	107
	$\mathrm{HepG2}^e$	69 $\mu g \text{ mL}^{-1} \left(\text{IC}_{50} \right)$	106		$\mathrm{L}1210^i$	12.73 $\mu g \text{ mL}^{-1} \left(\text{IC}_{50} \right)$	107
Compd 1	BGC-823	15.2 $\mu g \text{ mL}^{-1} (IC_{50})$	17	Compd 72	A549	$2.8 \mu M (IC_{50})$	49
	A549	5.93 μM (IC ₅₀)	49			25.8 μ M (LD ₅₀)	56
		45.8 μM (LD ₅₀)	56		SK-OV3	4.24 μM (IC ₅₀)	49
	SK-OV3 ^j	7.09 μM (IC ₅₀)	49			23.1 μ M (LD ₅₀)	56
		43.2 μ M (LD ₅₀)	56		HT-29	28.0 μ M (LD ₅₀)	56
	HT-29 ^k	41.4 μ M (LD ₅₀)	56		HL-60	29.5 μ M (LD ₅₀)	56
	HL-60	32.8 μ M (LD ₅₀)	56		AGS	15.2 μ M (LD ₅₀)	56
	AGS^l	32.8 μ M (LD ₅₀)	56	Compd 73	HCT-116	6.66 μM (IC ₅₀)	55
Compd 2	HCT-116 ^m	$3.9 \ \mu g \ mL^{-1} \left(IC_{50}\right)$	17		SMMC-7721	5.13 μM (IC ₅₀)	55
	SMMC-7721 ⁿ	6.9 $\mu g \text{ mL}^{-1} \left(\text{IC}_{50} \right)$	17		SGC-7901	3.63 μM (IC ₅₀)	55
	SGC-7901°	4.3 $\mu g \text{ mL}^{-1} (IC_{50})$	17		BGC-823	$3.11 \mu M (IC_{50})$	55
Compd 3	HCT-116	12.2 $\mu g \text{ mL}^{-1} (IC_{50})$	17	Compd 77	HCT-116	$2.8 \ \mu g \ mL^{-1} \left(IC_{50}\right)$	17
	SMMC-7721	8.9 $\mu g \text{ mL}^{-1} (IC_{50})$	17		SMMC-7721	8.8 $\mu g \text{ mL}^{-1} (IC_{50})$	17
Compd 4	HCT-116	4.1 $\mu g \text{ mL}^{-1} (IC_{50})$	17		SGC-7901	11.8 $\mu g \text{ mL}^{-1} (IC_{50})$	17
	SMMC-7721	4.2 $\mu g \text{ mL}^{-1} (IC_{50})$	17		BGC-823	$5.2 \ \mu g \ mL^{-1} \ (IC_{50})$	17
	SGC-7901	9.8 $\mu g \text{ mL}^{-1} (IC_{50})$	17	Compd 78	HCT-116	1.3 $\mu g \text{ mL}^{-1} (IC_{50})$	17
Compd 5	HCT-116	4.7 $\mu g \text{ mL}^{-1} (IC_{50})$	17	•	SMMC-7721	6.2 $\mu g \text{ mL}^{-1} (IC_{50})$	17
•	SMMC-7721	4.2 $\mu g \text{ mL}^{-1} (IC_{50})$	17		SGC-7901	$3.4 \ \mu g \ mL^{-1} \left(IC_{50}\right)$	17
	SGC-7901	$5.4 \ \mu g \ mL^{-1} \left(IC_{50}\right)$	17	Compd 84	A549	61.9 μM (LD ₅₀)	56
	BGC-823	1.6 $\mu g \text{ mL}^{-1} (IC_{50})$	17	1	SK-OV3	70.4 μM (LD ₅₀)	56
Compd 6	HCT-116	21.31 μM (IC ₅₀)	55		HT-29	46.3 μM (LD ₅₀)	56
•	SMMC-7721	50.7 μM (IC ₅₀)	55		HL-60	35.9 μM (LD ₅₀)	56
	SGC-7901	26.34 μM (IC ₅₀)	55		AGS	44.7 μM (LD ₅₀)	56
	BGC-823	17.62 μM (IC ₅₀)	55	Compd 129	SMMC-7721	32.04 μM (IC ₅₀)	55
Compd 7	HCT-116	1.8 $\mu g \text{ mL}^{-1} (IC_{50})$	17	1	SGC-7901	28.68 μM (IC ₅₀)	55
r	SMMC-7721	$2.7 \ \mu g \ mL^{-1} \ (IC_{50})$	17		BGC-823	26.90 μM (IC ₅₀)	55
	SGC-7901	3.4 $\mu g \text{ mL}^{-1} (IC_{50})$	17		U937	6.0 μM (IC ₅₀)	110
	BGC-823	1.6 $\mu g \text{ mL}^{-1} (IC_{50})$	17	Compd 130	HCT-116	24.37 μM (IC ₅₀)	55
Compd 9	SMMC-7721	11.7 $\mu g \text{ mL}^{-1} (IC_{50})$	17		SMMC-7721	28.94 μM (IC ₅₀)	55
compa s	SGC-7901	1.8 $\mu g \text{ mL}^{-1} (IC_{50})$	17		SGC-7901	65.86 μM(IC ₅₀)	55
	BGC-823	9.2 $\mu g \text{ mL}^{-1} (IC_{50})$	17		BGC-823	28.68 μM (IC ₅₀)	55
Compd 19	A549	61.7 μM (LD ₅₀)	56	Compd 143	U937	0.8 μM (IC ₅₀)	111
compu 15	SK-OV3	74.5 μM (LD ₅₀)	56	00mpu 110	HeLa	0.8 μM (IC ₅₀)	111
	HT-29	50.7 μM (LD ₅₀)	56	Compd 145	P388 ^p	3.3 $\mu g \text{ mL}^{-1} (IC_{50})$	30
	HL-60	40.8 μM (LD ₅₀)	56	Compd 149	P388	6.2 $\mu g \text{ mL}^{-1} (IC_{50})$	30
	AGS	49.5 μM (LD ₅₀)	56	Compd 152	U937	10.0 μM (IC ₅₀)	109
Compd 20	A549	16.3 μM (LD ₅₀)	56	Compd 158	P388	15.0 $\mu g \text{ mL}^{-1} (IC_{50})$	30
30mpu 2 0	SK-OV3	23.8 μM (LD ₅₀)	56	Compd 161	$CRL1579^q$	3.65 μM (EC ₅₀)	16
	HT-29	20.7 μM (LD ₅₀)	56	compa 101	LOX-IMVI ^r	11.99 μM (EC ₅₀)	16
	HL-60	6.2 μM (LD ₅₀)	56		MOLT-4F ^s	2.65 μM (EC ₅₀)	16
	AGS	4.7 μM (LD ₅₀)	56		$KM12^t$	13.70 μM (EC ₅₀)	16
Compd 21	HCT-116	26.05 μM (IC ₅₀)	55		UO-31 ^u	6.99 μM (EC ₅₀)	16
Compu 21	SMMC-7721	38.32 μM (IC ₅₀)	55	Compd 162	CRL1579	13.12 μM (EC ₅₀)	16
	SGC-7901	32.04 μM (IC ₅₀)	55	Compu 102	LOX-IMVI	31.26 μM (EC ₅₀)	16
	BGC-823	40.24 μM (IC ₅₀)	55		MOLT-4F	23.07 μM (EC ₅₀)	16
Compd 24	HCT-116	5.50 μM (IC ₅₀)	55		KM12	1 11	
Compu 24		. ()	55		UO-31	28.05 μM (EC ₅₀)	16
	SMMC-7721 SGC-7901	5.67 μM (IC ₅₀)		Commd 162		9.78 μM (EC ₅₀)	16
		3.07 μM (IC ₅₀)	55 55	Compd 163	CRL1579	3.34 μM (EC ₅₀)	16
Compd 28	BGC-823	2.82 μM (IC ₅₀) 3.15 μM (IC ₅₀)	55 49		LOX-IMVI MOLT-4F	13.46 μM (EC ₅₀)	16 16
Compu 28	A549					7.62 μM (EC ₅₀)	16
	CV OV2	33.5 μM (LD ₅₀)	56 40		KM12	13.84 μM (EC ₅₀)	16
	SK-OV3	4.72 μM (IC ₅₀)	49	Compd 164	UO-31	16.82 μM (EC ₅₀)	16
	LIT 20	38.0 μM (LD ₅₀)	56 56	Compd 164	CRL1579	9.50 μM (EC ₅₀)	59
	HT-29	11.4 μM (LD ₅₀)	56 56		LOX-IMVI	16.60 μM (EC ₅₀)	59
	HL-60	8.6 μM (LD ₅₀)	56 56		MOLT-4F	8.90 μM (EC ₅₀)	59
Camard 20	AGS	3.9 μ M (LD ₅₀)	56		KM12	5.00 μM (EC ₅₀)	59 50
Compd 29	HCT-116	3.4 $\mu g \text{ mL}^{-1} (\text{IC}_{50})$ 5.1 $\mu g \text{ mL}^{-1} (\text{IC}_{50})$	17	Q 1 4 6 =	UO-31	5.20 μM (EC ₅₀)	59 50
	SMMC-7721	5.1 ug ml. 1 (IC.a)	17	Compd 165	CRL1579	2.90 μM (EC ₅₀)	59

Table 4 (Contd.)

Sample	Model	Active concentration	Ref.	Sample	Model	Active concentration	Ref.
	SGC-7901	9.5 $\mu g \text{ mL}^{-1} (IC_{50})$	17		LOX-IMVI	12.50 μM (EC ₅₀)	59
	BGC-823	2.6 $\mu g \text{ mL}^{-1} (IC_{50})$	17		MOLT-4F	10.7 μM (EC ₅₀)	59
	A549	11.8 μM (LD ₅₀)	56		KM12	11.9 μM (EC ₅₀)	59
	SK-OV3	14.6 μM (LD ₅₀)	56		UO-31	7.60 μM (EC ₅₀)	59
	HT-29	12.1 μ M (LD ₅₀)	56	Compd 202	HL-60	18.0 μM (IC ₅₀)	87
	HL-60	8.2 μM (LD ₅₀)	56	Compd 205	HL-60	4.3 μM (IC ₅₀)	87
	AGS	4.1 μM (LD ₅₀)	56	Compd 215	HL-60	6.7 μM (IC ₅₀)	87
Compd 67	A549	57.8 μM (LD ₅₀)	56	Compd 222	HL-60	5.1 μM (IC ₅₀)	87
	SK-OV3	71.3 μM (LD ₅₀)	56	Compd 225	HL-60	8.8 μM (IC ₅₀)	87
	HT-29	65.0 μM (LD ₅₀)	56	Compd 226	HL-60	10.1 μM (IC ₅₀)	87
	HL-60	45.2 μ M (LD ₅₀)	56	Compd 227	HL-60	5.2 μM (IC ₅₀)	87
	AGS	43.9 μM (LD ₅₀)	56	Compd 246	P388	$0.18~\mu g~m L^{-1}~(IC_{50})$	30
Compd 184	HL-60	9.5 μM (IC ₅₀)	87	Compd 254	HL-60	4.3 μM (IC ₅₀)	87

^a HL-60 = promyelocytic leukemia cell line. ^b U937 = human leukemia cell line. ^c HeLa = human carcinoma cell line. ^d MCF-7 = human breast cancer cell line. ^e HepG2 = human hepatoma cell line. ^f MDA-MB-231 = human breast cancer cell line. ^g BGC-823 = stomach cancer cell line. ^h A549 = lung carcinoma cell line. ^l L1210 = mouse leukemia cell line. ^j SK-OV3 = human ovarian cancer cell line. ^k HT-29 = human colon carcinoma cell line. ^l AGS = human lung cancer cell line. ^m HCT-116 = human colon carcinoma cell line. ⁿ SMMC-7721 = human hepatocellular carcinoma cell line. ^o SGC-7901 = human gastric cancer cell line. ^p P388 = mouse leukemia cell line. ^q CRL1579 = human skin cancer cell line. ^r LOX-IMVI = human melanoma cell line. ^s MOLT-4F = human leukemia cell line. ^t KM12 = human colon carcinoma cell line. ^u UO-31 = human renal cell line.

4′-O-methylalpinumisoflavone, and alpinumisoflavone inhibited MAO in a concentration-dependent manner, with IC $_{50}$ values of 19.4, 23.9, and 25.8 μM, respectively. Of these, gancaonin A exhibited a selective inhibitory effect against MAO-B (IC $_{50} = 0.8$ μM) in comparison with MAO-A (IC $_{50} > 800$ μM). ¹¹⁸ CTXA, cudraflavanone A and cudraflavone B exhibited moderate inhibitory effects against mouse brain MAO, with IC $_{50}$ values of 88.3, 89.7, and 80.0 μM, respectively. ⁵⁰

The neuroprotective potential of the flavonoids orobol (230), 6-prenylorobol (255) and 6,8-diprenylorobol was evaluated via enhancing the ubiquitin/proteasome-dependent degradation of α -synuclein and synphilin-1 in SH-SY5Y human neuroblastoma cells induced by 6-hydroxydopamine (6-OHDA) (Table 5), which signified that they might be possible candidates for the treatment of neurodegenerative diseases. 119 5,7-Dihydroxychromone (426) could prevent 6-OHDA-induced oxidative stress and apoptosis in SH-SY5Y cells via the activation of the Nrf2/ARE

Table 5 Neuroprotective activity of compounds against 6-OHDA-induced SH-SY5Y cells

Compd	$EC_{50}\left(\mu M\right)$	Ref.	Compd	$EC_{50}\left(\mu M\right)$	Ref.
17	4.5	27	142	9.1	145
28	8.2	27	227	15.2	119
39	7.2	27	228	18.5	119
43	16.6	27	230	6.4	119
44	2.4	27	254	10.1	119
45	2.2	27	255	4.5	119
51	0.8	27	305	9.2	145
64	3.0	27	311	8.0	145
74	15.5	27	322	12.9	145
75	0.7	27	343	6.2	145
91	2.3	27	416	11.2	168
97	5.1	27	419	30.2	145
103	15.5	145	426	1.9	145

signalling pathway and the overexpression of antioxidant enzymes, including HO-1, NAD(P)H: quinone oxidoreductase and the glutamate-cysteine ligase catalytic subunit. 120 In LPSstimulated BV2 mouse microglia, CTXA ($IC_{50} = 0.98 \mu M$) decreased the production of TNF-α, IL-1β, and IL-12, inhibited the phosphorylation and degradation of IκB-α, and blocked the nuclear translocation of p50 and p65 by inhibiting the NF-κB and MAPK pathways. 121 Cudraflavanone D (132) could suppress the production of NO in LPS-induced BV2 microglial cells with an IC50 value of 6.28 µM and exert anti-neuroinflammatory activity by targeting iNOS and COX-2 via the MAPK and NF-κB pathways. Demethylsuberosin (299), as a potent proteasome activator, attenuated the 1-methyl-4-phenylpyridinium-induced dysfunction of the chymotrypsin-like and caspase-like activities of proteasomes in SH-SY5Y cells with EC₅₀ values of 0.76 μM and 0.82 µM, respectively, and protected SH-SY5Y cells against 1-methyl-4-phenylpyridinium-induced cell death, with an EC₅₀ value of 0.17 μM.¹²² 4'-O-Methylalpinumisoflavone isolated from C. tricuspidata fruits exerted anti-neuroinflammatory effects against LPS-induced microglial activation in BV2 cells by decreasing NF-kB signalling and the phosphorylation of MAPKs.123 The above results demonstrated that those compounds with neuroprotective activities could be considered as candidates for further research for therapeutic purposes into neurodegenerative diseases such as Parkinson's disease.

4.6. Antiobesity activity

Excess body weight and obesity are severe threats to public health worldwide. The leaves of C. tricuspidata, in comparison with other parts, exhibited the most pronounced inhibitory effect against pancreatic lipase (PL), which is a key enzyme for lipid absorption, with an IC₅₀ value of 9.91 μ g mL⁻¹ in vitro, and were able to reduce plasma triacylglycerol levels and delay

dietary fat absorption in vivo.18 The optimal conditions for the maximum PL-inhibiting activity and extraction yield of C. tricuspidata fruits were determined using response surface methodology to be an ethanol concentration of 74.5%, a temperature of 61.9 °C, and an extraction time of 13.5 h.¹² Flavonoids isolated from C. tricuspidata, namely, cudraflavanones A and D and 5,7,4'-trihydroxy-6,8-diprenylisoflavone, inhibited PL, with IC₅₀ values of 9.0, 6.5, and 65.0 µM, respectively.12,124 Further SAR studies highlighted that the prenyl moiety and number and position of hydroxyl groups of the flavonoids seemed to affect the PL-inhibiting activity, which needs to be clarified using more derivatives. The PL-inhibiting activity of C. tricuspidata fruits has been proven to vary with their maturation stage.66 Unripe fruits of C. tricuspidata, in accordance with their higher content of total phenolic compounds and flavonoids, exhibited stronger PL-inhibiting activity in comparison to ripe fruits.66 In addition, an isoflavone, namely, cudracusisoflavone B (195), from unripe fruits exhibited strong PL-inhibiting activity, with an IC₅₀ value of 16.8 μM , in a non-competitive manner. 66 Therefore, the maturation stage is an important factor for the efficacy, and unripe fruits appeared to be a good source of agents for the regulation of obesity. Protein-tyrosine phosphatases (PTP1B) are also important risk factors for obesity-related metabolic diseases. The leaves of C. tricuspidata displayed a strong inhibitory effect against PTP1B and substantially inhibited fat accumulation in 3T3-L1 cells in a dose-dependent manner.19 Xanthones and flavonoids isolated from the roots of C. tricuspidata, including CTXA, cudratricusxanthones L (12) and N (14), cudracuspixanthone A, cudraxanthones D, L, and M, macluraxanthone B, 1,6,7-trihydroxy-2-(1,1-dimethyl-2-propenyl)-3-

methoxyxanthone (87), cudraflavone C (105), kuwanon C (114), cudraflavanone D and euchrestaflavanone C, displayed a significant inhibitory activity against PTP1B in a dosedependent manner, with IC₅₀ values ranging from 1.9 to 13.6 μM.¹²⁵ In comparison with flavonoids, prenylated xanthones displayed stronger PTP1B-inhibiting effects, which suggested that they may be promising agents for the future discovery of novel PTP1B inhibitors.

An aqueous extract of C. tricuspidata leaves that underwent fermentation mediated by lactic acid bacteria was proven to be beneficial for promoting osteogenic differentiation of osteoblastic cells and inhibiting fat accumulation in adipocytes.99 In diet-induced obesity (DIO) mice, this extract could decrease levels of aspartate aminotransferase, alanine aminotransferase, total fat mass, triglycerides, and blood glucose and was also found to promote the phosphorylation of IRS-1 and Akt in liver tissues and improve insulin secretion.19 Correspondingly, the leaves of C. tricuspidata could be used as materials to produce a functional food product with antiobesity effects. 126 6,8-Diprenylgenistein, which is a flavonoid isolated from C. tricuspidata, was proven to decrease body weight, epididymal fat and serum triglyceride levels in DIO mice.127 The underlying mechanism of this compound has been demonstrated, namely, that it could inhibit lipogenic genes by the regulation of transcription factors such as peroxisome proliferator-activated receptor γ (PPAR γ) and CCAAT/enhancer-binding protein α (C/EBP α) and

hormones such as leptin and adiponectin. 127 6,8-Diprenylgenistein was also found to regulate acetyl-CoA carboxylase (ACC) and hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) by the activation of AMP-activated protein kinase (AMPK).127 Further investigation is warranted to determine whether their beneficial effects are associated with gut microbiota, which is a topic of recent and growing interest.

4.7. Immunomodulatory effects

Emerging evidence has suggested that *C. tricuspidata* is a potent immunomodulator. An aqueous extract of C. tricuspidata displayed potent adjuvant activity to enhance antigen-specific antibody responses and cellular immune responses against keyhole limpet hemocyanin. 128 In recent years, plant polysaccharides have emerged as an important class of bioactive natural products that are ideal therapeutic candidates for immunomodulatory functions with low toxicity. The in vitro immunomodulatory activities of the polysaccharides from C. tricuspidata roots were investigated in relation to the activation of mouse peritoneal macrophages.71,74 The results showed that the four water-soluble polysaccharides, namely, CTPS-1A, CTPS-2B, CTPS-3A, and CTP-B1, could directly stimulate the proliferation of mouse splenocytes alone or in combination with concanavalin A or LPS within the concentration range of 6.25 to 100 µg mL⁻¹, in a comparable way to the immunomodulator lentinan. 71,74 T-helper type 1 (Th1) and Th2 cytokines have been demonstrated to interact reciprocally to maintain a balanced immune network. The C. tricuspidata glycoprotein could prevent the development of immune diseases related to Th2 cell responses, such as autoimmune diseases, viral infections, and allergies.36,129 The precise mechanism of the differentiation of Th cells into Th1 or Th2 cells as induced by the C. tricuspidata glycoprotein remains to be elucidated.

4.8. Antiatherosclerotic activity

CTXA from C. tricuspidata was found to exert inhibitory effects on the synthesis and proliferation of DNA in vascular smooth muscle cells stimulated by platelet-derived growth factor (PDGF)-BB by suppressing the PDGF receptor β-chain and downregulating the Ras-Raf-MEK-ERK1/2 signalling pathways, and may serve as an antiatherosclerotic lead compound.80 Likewise, cudraflavanone A was useful in the prevention of atherosclerosis or restenosis after angioplasty, and the molecular mechanism was found to be that it inhibited the PDGF-BBinduced growth of rat aortic smooth muscle cells via an Aktdependent pathway.81 In addition, cudraflavone B was observed to inhibit the proliferation of rat aortic smooth muscle cells by inducing the expression of p21cip1 and p27kip1 and subsequent cell cycle arrest with a reduction in the phosphorylation of pRb at the G1-S phase, which suggests its therapeutic potential for treating cardiovascular disease.9 Low-density lipoprotein (LDL) has been known to play a crucial role in the development of atherosclerosis and hypercholesterolemia. 130 Many compounds isolated from C. tricuspidata have been confirmed to be effective in preventing the oxidation of LDL in a TBARS assay (Table 3).

4.9. Antimicrobial activity

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The essential oil of *C. tricuspidata* fruits was proven to be able to disrupt the membrane functions of both Gram-positive and Gram-negative bacteria, which led to its effective use as a natural antimicrobial agent to control food-borne pathogens in the food industry. The antibacterial activity of the essential oil was investigated against Bacillus cereus ATCC 13061, Staphylococcus aureus ATCC 12600, Listeria monocytogenes ATCC 7644, Salmonella typhimurium ATCC 43174 and Escherichia coli O157:H7 ATCC 43889.76 The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the essential oil were in the range of 250-500 µg mL⁻¹ and 500-1000 μg mL⁻¹, respectively.⁷⁶ In addition, a methanolic extract of C. tricuspidata roots exhibited high antifungal activity against Gymnosporangium haraeanum Syd., Pyricularia oryzae Cav., Rhizoctonia solani Kühn, and Colletotrichum graminicola (Ces.) Wilson, with EC₅₀ values of 803, 997, 981 and 930 $\mu g \text{ mL}^{-1}$, respectively.11

4.10. Skin protection

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by elevated immunoglobulin E (IgE) levels, mast cell infiltration and skin lesions including pruritus, erythema and eczema.¹³¹ An ethanolic extract of *C. tricuspidata* stems could be applied topically to decrease serum IgE levels and mast cell counts in the dermis of the skin in an AD-like NC/Nga mouse model induced by *Dermatophagoides farinae* extract.¹³¹ Similarly, an aqueous extract of *C. tricuspidata* fruits was also found to inhibit the development of AD-like skin lesions induced by repeated applications of *D. farinae* in sensitized NC/Nga mice by reducing plasma concentrations of mouse thymus and activation-regulated chemokine (mTARC), histamine and IgE.¹³² Nevertheless, the definite active compounds responsible for the anti-atopic dermatitis activity remain to be identified.

A methanolic extract of C. tricuspidata stems was demonstrated to prevent skin inflammation and skin aging via suppressing the solar ultraviolet-induced expression of COX-2.82 The EtOAc fraction (IC₅₀ = 24.4 ppm) and the *n*-BuOH fraction (IC₅₀ = 88.3 ppm) of the C. tricuspidata stem extract could reduce the activity of tyrosinase and the melanin content in a concentrationdependent manner.79 It was found that the flavonoids steppogenin (149, $IC_{50} = 2.52 \mu M$) and trans-dihydromorin (160, $IC_{50} =$ 21.54 μ M) and the phenylpropanoid oxyresveratrol (IC₅₀ = 2.85 μM) from the twigs of C. tricuspidata displayed potent inhibitory activities against mushroom tyrosinase and the melanogenesis process in melanocytes, which suggested their potential to be developed as skin-whitening agents in cosmetics and antibrowning agents in food.75 The tyrosinase-inhibiting activity of the flavonoids could be affected by the hydroxyl groups substituted at the 2- and 4-positions of the aromatic ring.⁷⁵ Oxyresveratrol and trans-dihydromorin, as hypopigmenting agents, post-transcriptional degradation microphthalmia-associated transcription factor (MITF), leading to significant decreases in the production of tyrosinase-related protein 1 (TRP-1) and tyrosinase-related protein 2 (TRP-2) in b16 and melan-a cells.133 Besides, 6,8-diprenylorobol and

pomiferin (233) could inhibit the photooxidation of A2E, which is an important constituent of lipofuscin in the retinal pigment epithelium, in a dose-dependent manner.³² Collectively, these studies clearly showed that *C. tricuspidata* and the isolated bioactive compounds could be used as cosmeceutical materials and food constituents for the promotion of skin health.

4.11. Antidiabetic activity

Lee et al.20 reported that the aqueous extract of C. tricuspidata leaves could significantly improve hepatic insulin resistance and hyperglycemia by controlling obesity-induced stress in the hepatic endoplasmic reticulum and inflammation in the liver of db/db mice. Furthermore, an in vitro study demonstrated that both C. tricuspidata leaves and the isolated compound kaempferol could reduce hepatic insulin resistance by suppressing insulin receptor substrate signalling and the inflammatory response in HepG2 cells induced by endoplasmic reticulum stress.134 In addition, the α-glucosidase-inhibiting activities of aqueous extracts of C. tricuspidata stems and roots depended on the harvesting time and climate.21 A root extract exerted potent inhibitory effects on α-glucosidase activity, with 77% inhibition at a concentration of 300 μg mL⁻¹, which signified that the root could serve as an antidiabetic biomaterial.21 Xanthones, including CTXA, cudratricusxanthone F, cudraxanthones D and L, macluraxanthone B, 1,3,6,7-tetrahydroxy-2-(3-methylbut-2-enyl)-8-(2-methylbut-3-en-2-yl)-9*H*-xanthen-9-one (83) and 1,3,7-trihydroxy-4-(1,1-dimethyl-2-propenyl)-5,6-(2,2-dimethylchromeno)xanthone (84), displayed inhibitory activities against α-glucosidase, with IC₅₀ values of 16.2-52.9 μM.⁵² CTXA was also proven to prevent the production of NO, the expression of iNOS, and the activation of JAK/STAT and NF-kB in RINm5F cells induced by IL-1β and IFN-γ and to inhibit the glucosestimulated secretion of insulin in pancreatic islets.135 The above results suggested that C. tricuspidata may be a promising therapeutic material in the treatment of diabetes.

4.12. Others

Besides the above pharmacological properties, other biological activities of *C. tricuspidata* have also been reported. An aqueous extract of *C. tricuspidata* stems could decrease systolic blood pressure in hypertension induced by N^G -nitro-L-arginine methyl ester, in part by enhancing the generation of vascular NO/cGMP and the amelioration of renal functions. The anticoagulant activity of CTXA was investigated by Yoo *et al.*, 9 who revealed that CTXA could inhibit the generation of cell-based thrombin, activated factor X (FXa) and thrombin and exhibited thrombolytic activity by decreasing the ratio of plasminogen activator inhibitor type 1 (PAI-1) to tissue-type plasminogen activator (t-PA).

Park *et al.*⁵³ revealed that xanthones bearing 6,7 vicinal dihydroxy groups on the A ring, including CTXA, cudratricusxanthone F, cudraxanthones D, L and M, macluraxanthone B, and 1,3,6,7-tetrahydroxy-2-(3-methylbut-2-enyl)-8-(2-methylbut-3-en-2-yl)-9H-xanthen-9-one, displayed nanomolar inhibitory activity (IC₅₀: 80–270 nM) against neuraminidase. Cudraflavanone A, which bears a C-8 hydrated prenyl group,

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also displayed high neuraminidase-inhibiting activity, with an IC₅₀ of 380 nM.¹³⁷ This implied that these xanthones and flavonoids may be potential antiviral agents in the future.

The above descriptions indicated that many compounds have a variety of activities, in particular CTXA, which is a major and important component with a wide range of activities. Recently, pharmacokinetic studies of representative constituents of C. tricuspidata have also attracted attention. The in vitro metabolic profiling of CTXA in human liver microsomes has been recently investigated, which revealed that eight identified metabolites of CTXA were involved with cytochrome P450 enzymes (CYPs) and uridine 5'-diphospho-glucuronosyltransferase enzymes (UGTs).138 In a follow-up study, CTXA has been demonstrated to exhibit reversible competitive inhibition of CYP1A2 and CYP2C9 and non-competitive inhibition of CYP2C8 in human liver microsomes, which has begun to shed light on the in vivo metabolism of CTXA.139 Cudratricusxanthone B, as another example, has also been investigated for its pharmacokinetics by a fast and sensitive HPLC-MS/ MS method, but its oral bioavailability (OB) remains unclear and merits future investigation. 140 Therefore, it is suggested that the pharmacokinetics of this plant should be studied systematically.

Conclusions

This review provides an up-to-date and comprehensive summary concerning the botany, traditional uses, phytochemistry and pharmacology of the traditional folk medicine C. tricuspidata. As a medicinal plant, C. tricuspidata has been used to treat rheumatism, bruising, scabies, hepatitis, jaundice, gonorrhea, dysmenorrhea and amenorrhea in East Asia for thousands of years. During the last few decades, C. tricuspidataderived extracts and compounds have attracted much attention for their promising biological activities, including antiantioxidant, antitumor, hepatoprotective, inflammatory, immunomodulatory, neuroprotective, antiobesity, antimicrobial, antiatherosclerotic, skin-protecting, and antidiabetic activities. Obviously, some pharmacological activities are not related to the traditional uses of this species but provide valuable hints for new areas of application. Xanthones and flavonoids are the two major classes of constituent that contribute either directly or indirectly to the biological effects of C. tricuspidata, followed by minor classes, including organic acids, polysaccharides, phenylpropanoids, and others. Findings and knowledge regarding the phytochemistry and pharmacology of C. tricuspidata have established a basis for further research on, and development of, this medicinal plant and its active components. Notably, the unique structures isolated from C. tricuspidata have aroused interest in research on the chemical and biogenic synthesis of these bioactive compounds that is suitable for large-scale preparation and molecular modification. This should be beneficial for the development and application of natural compounds from C. tricuspidata and their synthetic analogues. As a rich source of medicines and functional foods, quality control of C. tricuspidata is crucial to ensure both safety and efficacy. It is suggested that current advances, including mass spectrometry-based chemical profiling and DNA barcoding, should be used to authenticate, differentiate, and evaluate the quality of C. tricuspidata. Importantly, a common international criterion should be established with the ultimate goal of ensuring the effectiveness and safety and maximizing the medicinal benefits of C. tricuspidata.

As recent insights into the pharmacological mechanisms of C. tricuspidata are limited to in vitro bioassays of a limited number of molecules, it is essential and urgent to investigate the mechanisms of the bioactive extracts/isolates in appropriate animal models. To the best of our knowledge, few relevant data from clinical trials of C. tricuspidata (only in Chinese clinics) have been reported, and most clinical trials used a relatively small sample size and insufficient information. It is suggested that the efficacy of C. tricuspidata should be assessed in the future by combining its pharmacological effects, mechanisms of action and clinical applications. Detailed studies of the pharmacokinetics and toxicological properties and preclinical and clinical trials of C. tricuspidata are also eagerly awaited. More knowledge should be accumulated concerning the bioavailability, metabolism and toxicity of C. tricuspidata, which will be valuable for understanding its dosage efficacy and in vivo effects. It should be noted that the interaction between the bioactive constituents of C. tricuspidata and the human microbiota is an underappreciated aspect, as the gut microbiota plays a vital role in the pathogenesis and progression of obesity, diabetes and related metabolic disorders.141 Current findings have demonstrated that C. tricuspidata may serve as a good source of prebiotics that promote the growth of probiotic bacteria and improve the antioxidant activity of dairy products, which is of great interest for the development of functional foods.

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