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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 Asia[1] 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 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]

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 notable anti-inflammatory,[22,23] antitumor,[16,24] hepatoprotective,[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 anti-inflammatory[31] and antioxidant[32] 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 immunomodulatory[36] 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,

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Scopus, ACS, Web of Science, ScienceDirect, China Knowledge Resource Integrated Database (CNKI), Google Scholar, SciFinder 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.

2 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).[6] 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 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.

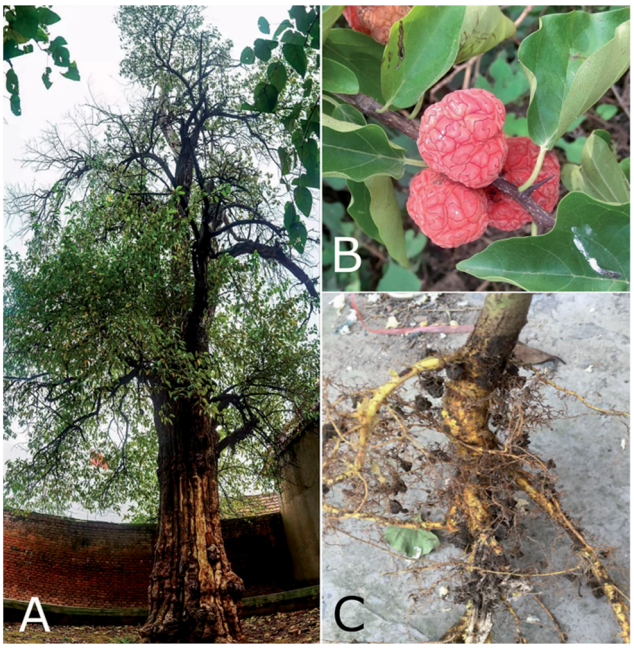

Fig. 1 Whole plant (~200 years) (A), fruits (B) and roots (C) of *C. tricuspidata*.

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 its diverse biological effects, *e.g.*, antioxidant, anti-inflammatory 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]

3 Phytochemistry

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

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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 anti-inflammatory,[22] antitumor,[17] neuroprotective,[51] hepatoprotective,[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 non-enzymatic manner[54] 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-(1,1-dimethyl-2-propenyl)-5,6-(2,2-dimethylchromeno)xanthone (**84**), exhibited both potent superoxide- and hydroxyl radical-scavenging activities, which could be rationalized by their chelating effect with Fe^{2+} 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 well-defined 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 neuroprotective[62] 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 *ortho*-position 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 μg g^{-1}) followed by 2-acetylpyrrole (**405**, 1.86 μg g^{-1}), whereas the root extract was found to have *n*-hexanoic acid (13.13 μg g^{-1}) in the greatest concentration followed by *n*-heptanoic acid (**279**, 2.05 μg g^{-1}).[10] 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

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Table 1 Chemical constituents of *C. tricuspidata*

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

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Table 1 (*Contd.*)

No.	Compound name(s)	Tissue(s)	Ref.
63	Gerontoxanthone A	Root bark	25
64	Gerontoxanthone C	Root bark	27
65	Gerontoxanthone I	Roots	88
66	Isocudraniaxanthone A	Roots	116
67	Isocudraniaxanthone B	Root bark	56
68	Isocudraxanthone K	Root bark	25
69	Isogentisin	Roots	88
70	Isoalvaxanthone	Roots	88
71	Laxanthone I	Root bark	116
72	Macluraxanthone B	Whole plant	49
73	Macluraxanthone C	Roots	55
74	Nigrolineaxanthone F	Root bark	27
75	Neriifolone A	Root bark	27
76	Toxyloxanthone B	Root bark	145
77	Toxyloxanthone C	Roots	17
78	Xanthone V_{1a}	Roots	17
79	1-Trihydroxy-3,6,7-trimethoxyxanthone	Roots	55
80	1,3,5-Trihydroxy-4-prenylxanthone	Roots	116
81	1,3,5-Trihydroxy-2-(3-methylbut-2-enyl)xanthone	Root bark	27
82	1,3,5,6-Tetrahydroxyxanthone	Bark	149
83	1,3,6,7-Tetrahydroxy-2-(3-methylbut-2-enyl)-8-(2-methylbut-3-en-2-yl)-9*H*-xanthen-9-one	Roots	52
84	1,3,7-Trihydroxy-4-(1,1-dimethyl-2-propenyl)-5,6-(2,2-dimethylchromeno)xanthone	Roots	52
85	1,5-Dihydroxy-3,6-dimethoxyxanthen-9-one	Twigs	75
86	1,7-Dihydroxy-3,6-dimethoxyxanthone	Roots	55
87	1,6,7-Trihydroxy-2-(1,1-dimethyl-2-propenyl)-3-methoxyxanthone	Roots	119
88	1,6,7-Trihydroxy-3-methyl-4-(1,1,3-trimethyl-2-buten-1-yl)-9*H*-xanthen-9-one	Root bark	23
89	2-Deprenylrheediaxanthone B	Root bark	116
90	2,6-Dihydroxyxanthone	Roots	116
91	3-*O*-Methylcudratrixanthone G	Root bark	27
92	5-*O*-Methylformoxanthone C	Root bark	27
93	6-Deoxyisojacareubin	Root bark	27
94	6-Deoxy-γ-mangostin	Root bark	27
95	7-*O*-Demethylcudratrixanthone C	Root bark	145
96	8-Prenylxanthone	Roots	88
97	16-Hydroxycudratrixanthone Q	Root bark	145
98	16-Hydroxycudratrixanthone M	Root bark	145
99	16-Methoxycudratrixanthone M	Root bark	145
Flavonoids			
Flavones			
100	Artocarpesin	Roots and stems	17
101	Apigenin	Fruits	168
102	Apigenin-7-*O*-β-D-glucopyranoside	Fruits	168
103	Cudraflavone A	Root bark	150
104	Cudraflavone B	Root bark	150
105	Cudraflavone C	Root bark	151
106	Cudraflavone D	Root bark	151
107	Cudraflavone F	Roots	58
108	Cudraflavone G	Roots	58
109	Cudraflavone H	Root bark	145
110	Cycloartocarpesin B	Roots	17
111	Cyclomorusin	Twigs	75
112	Cycloartocarpin	Whole plant	152
113	Hirsutrin/quercetin-3-*O*-β-D-glucopyranoside	Fruits	66
114	Kuwanon C	Roots	125
115	Licoflavone C	Leaves	153
116	5,7,2′,4′-Tetrahydroxyflavone/norarthocarpetin	Stems	154
117	6-Prenylapigenin	Roots	58
118	Kaempferol	Root bark	134

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Table 1 (*Contd.*)

No.	Compound name(s)	Tissue(s)	Ref.
119	Kaempferol-3-*O*-β-D-glucopyranoside/astragalin	Fruits	168
120	Kaempferol-7-*O*-β-D-glucopyranoside/populnin	Whole plant	155
121	6-*p*-Hydroxybenzyl kaempferol-7-*O*-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-*O*-β-D-glucopyranoside/quercimeritrin	Root bark	158
127	6-*p*-Hydroxybenzyl quercetin-7-*O*-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
132	Cudraflavanone D	Roots	55
133	Cudraflavanone E	Roots	58
134	Cudraflavanone F	Roots	58
135	Cudraflavanone G	Root bark	145
136	(2*R*)-Cudraflavanone H	Root bark	145
137	(2*S*)-Cudraflavanone H	Root bark	145
138	Cycloaltilisin 7	Twigs	75
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
144	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
151	(2*S*)-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
158	Aromadendrin/dihydrokaempferol	Root bark and twigs	75 and 156
159	Dihydrokaempferol-7-*O*-β-D-glucoside	Twigs	75
160	*trans*-Dihydromorin	Twigs and whole plant	133 and 152
161	Gericudranin A	Stem bark	16
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-*O*-β-D-glucopyranoside	Twigs	75
169	Tricusposide	Bark	149
170	(2*S*,3*S*)-2,3-*trans*-Dihydromorin-7-*O*-β-D-glucoside	Twigs	75
171	(2*R*,3*R*)-2,3-Dihydro-3,5,6,7-tetrahydroxy-2-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one	Root bark	124
172	3,5,7,2′,4′-Pentahydroxydihydroflavonol	Whole plant	152
173	5,7,4′-Trihydroxy-8-*p*-hydroxybenzyldihydroflavonol	Root bark	124
Isoflavones			
174	Cudraisoflavone B	Fruits	28
175	Cudraisoflavone C	Fruits	28
176	Cudraisoflavone D	Fruits	28

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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	Fruits	28
183	Cudraisoflavone K	Fruits	28
184	Cudraisoflavone L (1)	Leaves	87
185	Cudraisoflavone L (2)	Fruits	168
186	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
222	Isolupalbigenin	Leaves	86
223	Isochandalone	Fruits	66
224	Lupiwighteone	Fruits	28
225	Lupalbigenin	Leaves	87
226	Laburnetin	Root bark	145
227	Millewanin H	Leaves	87
228	Millewanin G	Leaves	153
229	Osajin	Fruits	32
230	Orobol	Fruits	31
231	Oroboside	Fruits	66
232	Orobol-8-C-glucoside	Twigs	75
233	Pomiferin	Fruits	32
234	Parvisoflavone A	Root bark	145
235	Senegalensin	Fruits	31
236	Santal	Twigs	75
237	Sphaerobioside	Twigs	75
238	Ulexin B	Fruits	66
239	Ulexone B	Fruits	66

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Table 1 (*Contd.*)

No.	Compound name(s)	Tissue(s)	Ref.
240	Warangalon	Fruits	28
241	3′-*O*-Methylorobol	Root bark	124
242	4′-*O*-Methylalpinumisoflavone	Fruits and stem bark	105 and 116
243	4′-*O*-Methylcudraisoflavone O	Fruits	168
244	4′-*O*-Methylcudraisoflavone P	Fruits	168
245	4′-*O*-Methylerythrinin C	Fruits	168
246	4′,7-Dihydroxy-5-methoxyisoflavone/5-*O*-methylgenistein	Stems	154
247	5,3′-Dihydroxy-4′-methoxy-2″,2″-dimethylpyrano[5″,6″;6,7]isoflavone	Fruits	31
248	5,3′,4′-Trihydroxy-6″,6″-dimethylpyrano[2″,3″;7,6]isoflavone	Fruits	66
249	5,4′-Dihydroxy-8-(3″-methylbut-2″-enyl)-2‴-(4‴-hydroxy-4‴-methylethyl)furano[4‴,5‴;6,7]isoflavone	Fruits	31
250	5,4′-Dihydroxy-6-(3″-methylbut-2″-enyl)-2‴-(4‴-hydroxy-4‴-methylethyl)-3‴-methoxydihydrofurano[4‴,5‴;7,8]isoflavone	Fruits	31
251	5,7-Dihydroxy-6-(2″-hydroxy-3″-methylbut-3″-enyl)-4′-methoxyisoflavone	Fruits	31
252	5,7,4′-Trihydroxy-6,8-diprenylisoflavone/6,8-diprenylgenistein/8-(γ,γ-dimethylallyl)wighteone	Fruits	32 and 75
253	5,7,4′-Trihydroxydihydroisoflavone	Whole plant	152
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 acids			
258	Butyl citrate	Trunk	15
259	Benzoic acid	Fruits	76
260	Boric acid	Fruits	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
273	Tartaric acid	Fruits	70
274	*threo*-9,10-*O*-Isopropylidene-13-hydroxy-(11*E*)-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
279	*n*-Heptanoic acid	Roots	10
280	*n*-Octanoic acid	Roots	10
281	(*E*)-2-Decenoic acid	Roots	10
282	(*E*)-2-Octenoic acid	Roots and stems	10
283	2′,3′-Dihydroxypropyl pentadecanoate	Roots	165
284	4-Hydroxybenzoic acid	Fruits	168
285	9,12-Octadecadienoic acid	Trunk	15
286	9,12,15-Octadecatrienoic acid methyl ester	Trunk	15
287	9,12,15-Octadecatrien-1-ol	Trunk	15
288	9,17-Octadecadienal	Trunk	15
289	γ-Hexadecalactone	Root bark	145
Polysaccharides			
290	CTP-B1	Roots	73
291	CTPS-01	Roots	72

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Table 1 (*Contd.*)

No.	Compound name(s)	Tissue(s)	Ref.
292	CPS-0	Roots	71
293	CTPS-1A	Roots	71
294	CTPS-2B	Roots	71
295	CTPS-3A	Roots	71
Phenylpropanoids			
296	Bergapten	Root bark	145
297	Cudrastilbene	Roots	159
298	*cis*-3′,4′-Diisovalerylkhellactone	Root bark	145
299	Demethylsuberosin	Whole plant	163
300	Decursinol angelate	Root bark	145
301	Gomisin A	Roots	166
302	Gomisin H	Roots	166
303	Hyuganin C	Root bark	145
304	Imperatorin	Whole plant	163
305	Isoimperatorin	Whole plant	163
306	Oxyresveratrol	Twigs	75
307	Scopoletin	Trunk	15
308	Schizandrin	Whole plant	166
309	Syringaresinol	Whole plant	166
310	Umbelliferone	Root bark	151
311	Xanthyletin	Root bark	145
312	7-Hydroxy-2*H*-1-benzopyran-2-one	Trunk	15
313	5-Methoxy-4,5-diphenyl-2(5*H*)-furanone	Twigs	75
314	3-Methyl-2(5*H*)-furanone	Roots	10
315	5-Ethyl-2(5*H*)-furanone	Roots	10
316	5,5-Dimethyl-2(5*H*)-furanone	Roots	10
Other ingredients			
317	Betulin	Roots	165
318	Butyrospermol	Fruits	168
319	Camphene	Roots	10
320	Drimenol	Roots	10
321	Dihydroctinidiolide	Stems	10
322	Glutinol	Root bark	145
323	Lupeol	Roots	165
324	Lanosta-8-24-dien-3β-ol-acetate	Trunk	15
325	Lanosta-8-en-3-one	Trunk	15
326	Lanosta-7,24-diene-3β-ol	Whole plant	152
327	Lanosta-7,24-diene-3β-*O*-acetate	Whole plant	152
328	Olean-12-ene	Trunk	15
329	Taraxerone	Stems	160
330	Terpin hydrate	Roots	10
331	Ursolic acid	Roots	165
332	(*E*)-Geranylacetone	Roots	10
333	(*E*)-β-Ionone	Roots and stems	10
334	(*E*)-Linalool oxide	Roots	10
335	(*Z*)-Linalool oxide	Roots	10
336	(*E*)-α-Terpineol	Roots and stems	10
337	α-Amyrin	Root bark	145
338	Campesterol	Trunk	15
339	Daucosterol	Roots	165
340	Itesmol	Roots	165
341	β-Sitosterol	Roots	165
342	γ-Sitosterol	Trunk	15
343	Achilleol A	Whole plant	163
344	Antiarol	Fruits	76
345	Anisaldehyde	Roots	10
346	Aristolone	Trunk	15
347	Adacene 12	Fruits	76
348	Brosimine B	Root bark	145
349	Benzophenone	Stems	10
350	Benzylhydrazine	Fruits	76

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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
353	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-*N*-methylcarbamate	Fruits	76
367	Eriosematin A	Root bark	145
368	Ethyl *p*-*tert*-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
384	Salicylamide	Fruits	76
385	Scyllitol	Fruits	76
386	Sucrose	Bark	149
387	Stachydrine	Roots	167
388	Tridecanol	Fruits	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
398	1-Phenyl-1-cyclohexylethane	Fruits	76
399	1-Methyl-2-pyrrolidone	Roots and stems	10
400	1-[(2,4,6-Trimethylphenyl)methyl]imidazole	Fruits	76
401	(4*S*)-1,1-Difluoro-4 vinylspiropentane	Fruits	76
402	2-Deuteriophenylalanine	Fruits	76
403	2-Furanmethanol	Trunk	15
404	2-Ethyl-1-hexanol	Roots and stems	10
405	2-Acetylpyrrole	Stems	10
406	2,3-Dihydro-3,5-dihydroxy-6-methyl-4*H*-pyran-4-one	Trunk	15
407	2,4-Bis(4-hydroxybenzyl)phenol	Root bark and stems	10 and 145
408	2,5-Furandione	Trunk	15
409	3-Methoxycarbonylindole	Root bark	145
410	3-Methyl-2,5-furandione	Trunk	15
411	4-Acetylpyrazole	Roots	10
412	4-Ethylguaiacol	Roots and stems	10
413	4-Hydroxybenzalacetone	Root bark	145

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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	*p*-Hydroxybenzyl alcohol	Trunk	15
422	5-(Hydroxymethyl)-2-furancarboxaldehyde	Trunk	15
423	5-Hydroxy-2,2-dimethyl-2*H*,6*H*-benzodipyran-6-one	Root bark	124
424	5-Methyl-1*H*-pyrrole-2-carboxaldehyde	Stems	10
425	5,7-Dihydroxychromone	Root bark	124
426	6-Pentyl-5,6-dihydro-2*H*-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*.[72–74] 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.[74]

3.5. Phenylpropanoids (296–316)

Twenty-one phenylpropanoids have been reported in *C. tricuspidata*, 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-

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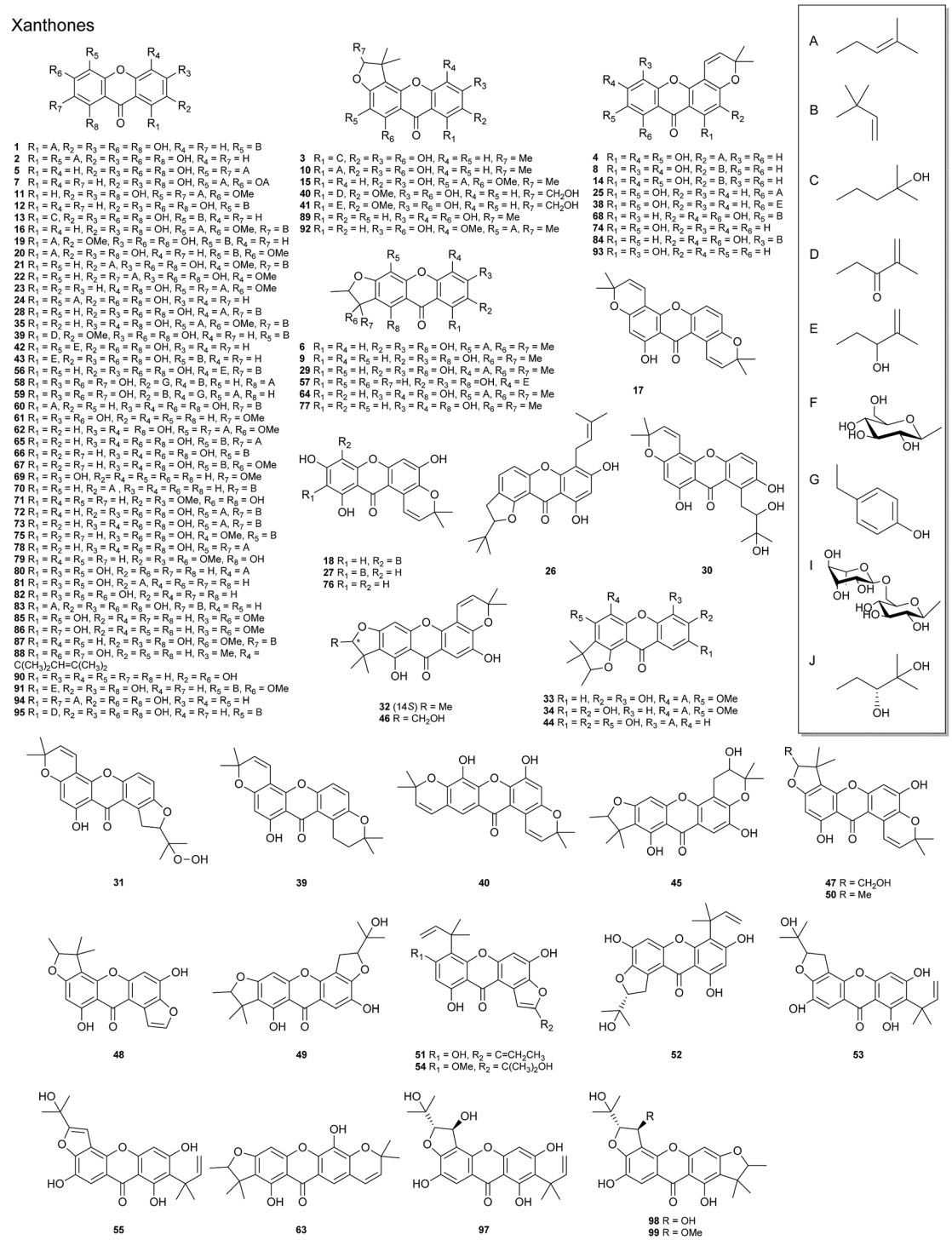

Fig. 2 Chemical structures of xanthones and flavonoids isolated from *C. tricuspidata*.

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 overproduction of nitric oxide (NO) and prostaglandin E_2 (PGE_2) 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-1β 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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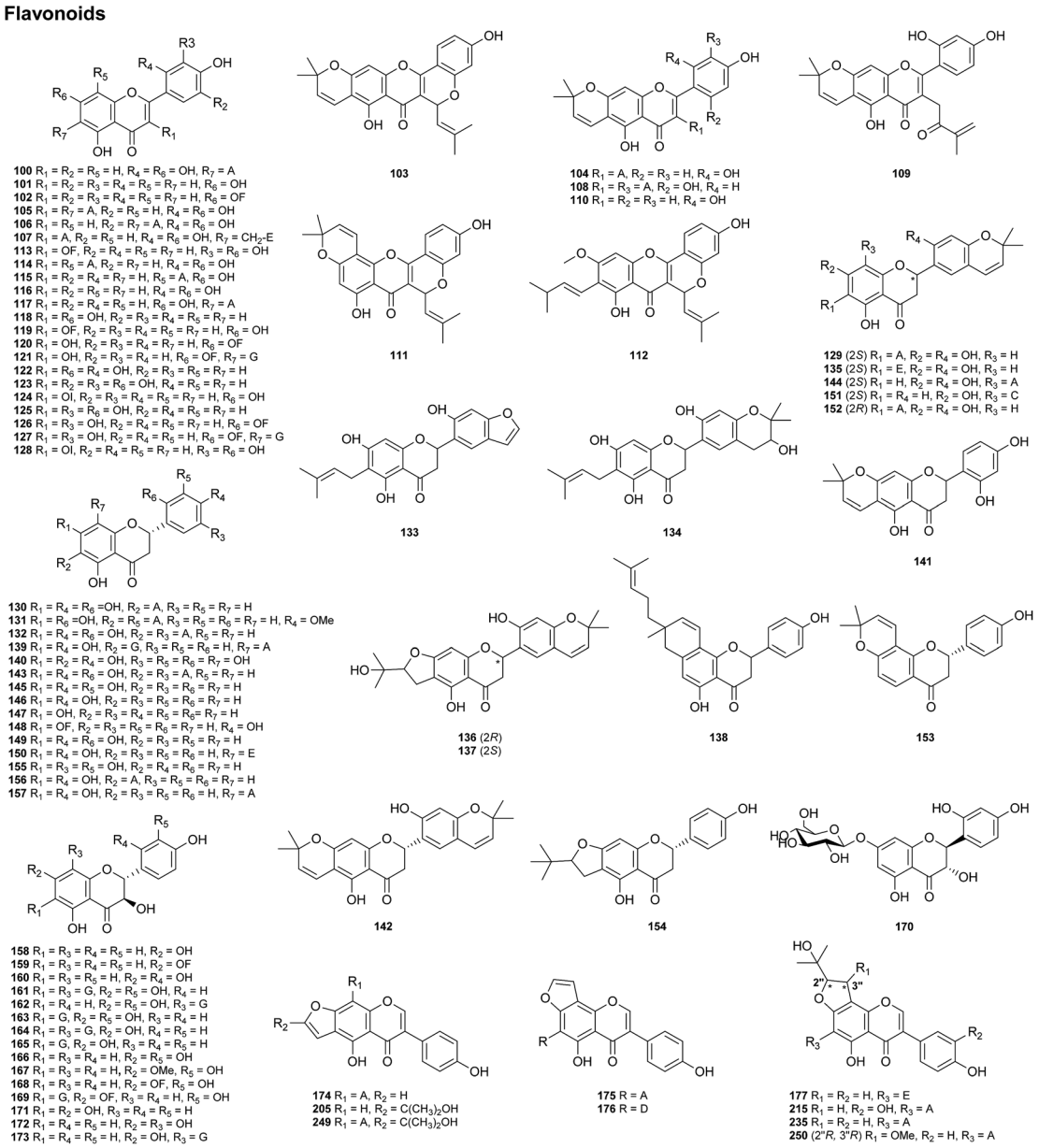

Fig. 2 *(contd.)*

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-κB (NF-κB).[84] The EtOAc fraction of *C. tricuspidata* stem bark could inhibit the differentiation of osteoclasts stimulated by IL-1β and mediated by receptor activator of NF-κB 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-1β, matrix metalloproteinases (MMPs), COX-2 and PGE_2 by inhibiting the phosphorylation of MAPK and the activation of NF-κB 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 ± 2.4%, 66.9 ± 1.8%, and 55.4 ± 2.7% at a concentration of 10 μM, 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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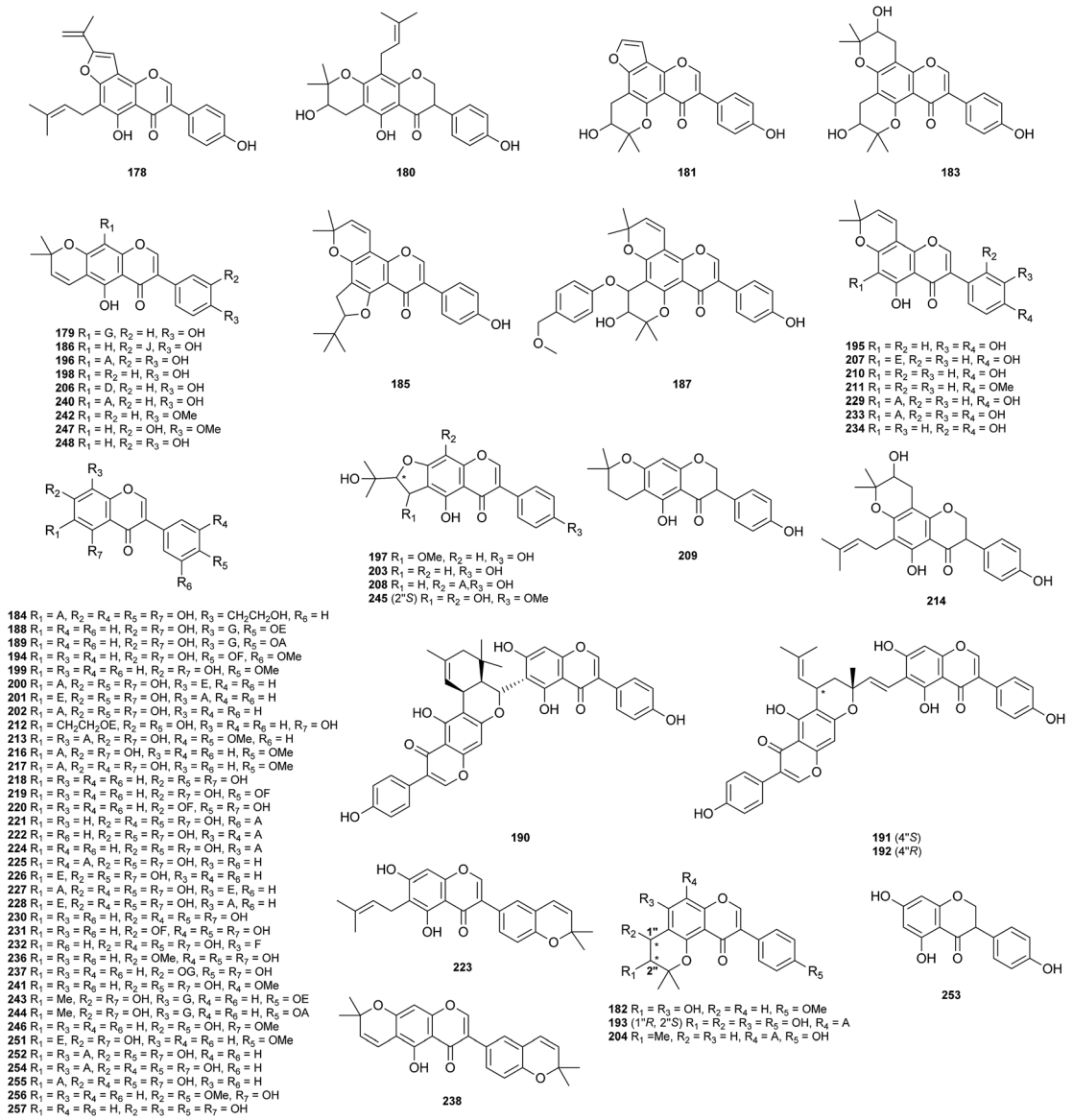

Fig. 2 *(contd.)*

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 PGE_2, NO, TNF-α, and IL-1β and increased the activity of HO in LPS-stimulated RAW 264.7 macrophages.[22] Moreover, CTXA could exert anti-soluble endothelial cell protein C receptor (anti-sEPCR) 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 non-steroidal 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 (FcεRI) and the expression of FcεRIβ mRNA but also inhibited the redistribution of F-actin and downstream signalling by suppressing the activation of FcεRI-mediated spleen tyrosine kinase in mast cells, which was suggestive of therapeutic potential for controlling mast cell activation in allergic processes.[91] Treatment with the *C. tricuspidata* glycoprotein resulted in degranulation for allergic response (β-hexosaminidase) and the activation of MAPK/activator protein-1 (AP-1) and NF-κB, as well as the expression of cytokines related to allergic inflammation (IL-4, IL-6, TNF-α, IFN-γ, and IL-1β), which are indirectly activated by bisphenol A or di(2-ethylhexyl) phthalate in HMC-1 and RBL-2H3 cells.[33,92–96]

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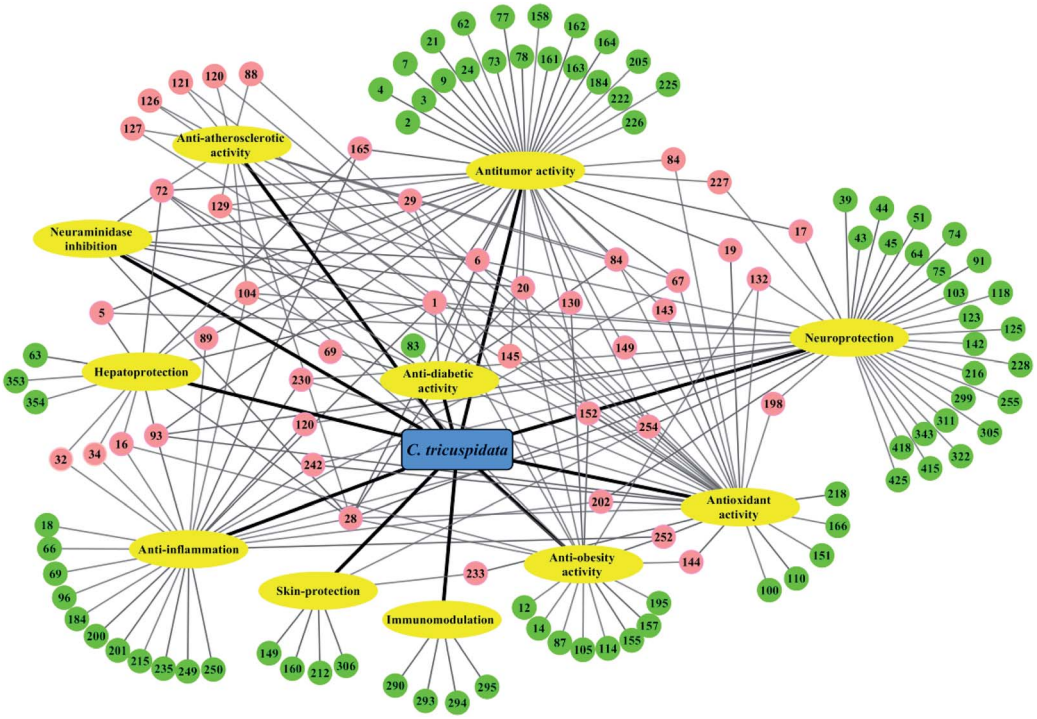

Fig. 3 Pharmacological activities of 124 active components from *C. tricuspidata*. The active compounds (circles) map ten pharmacological properties (yellow ovals). The pink circles represent multiple pharmacological properties. The green circles represent only one pharmacological property.

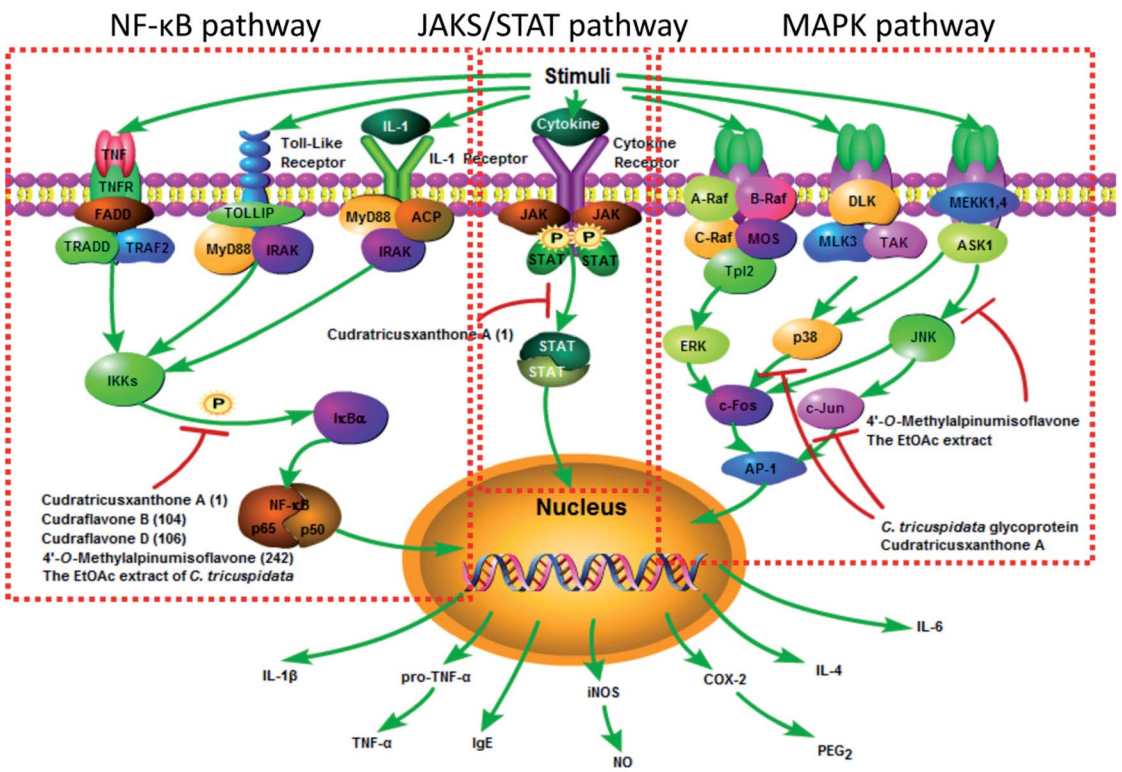

Fig. 4 Molecular mechanisms of anti-inflammatory extracts and compounds from *C. tricuspidata*.

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

Compd	IC_{50} (μM)	Ref.	Compd	IC_{50} (μM)	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′-azinobis(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 ± 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 mL^{-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 *n*-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 μM	23
Compd **29**	N.A	N.A	2.2 μM	23
Compd **67**	N.A	N.A	0.8 μM	23
Compd **72**	N.A	N.A	4.5 μM	23
Compd **84**	N.A	N.A	12.6 μM	23
Compd **88**	N.A	N.A	2.6 μM	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 μg mL^{-1}	N.A	3.65 μg mL^{-1}	156
Compd **121**	5.94 μg mL^{-1}	N.A	3.24 μg mL^{-1}	156
Compd **126**	4.04 μg mL^{-1}	N.A	3.72 μg mL^{-1}	156
Compd **127**	5.50 μg mL^{-1}	N.A	3.71 μg mL^{-1}	156
Compd **143**	>300 μM	5.4 μM	N.A	157
Compd **144**	>300 μM	6.0 μM	N.A	157
Compd **145**	N.A	N.A	3 μg mL^{-1}	30
Compd **149**	N.A	N.A	10 μg mL^{-1}	30
Compd **152**	>300 μM	8.3 μM	N.A	157
Compd **166**	N.A	N.A	6 μg mL^{-1}	30
Compd **230**	N.A	N.A	3 μg mL^{-1}	30
Compd **254**	>200 μM	16.3 μM	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 $CHCl_3$ 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 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 IC_{50} of 0.4 mM and inhibited the activity of protein kinase C with an IC_{50} of 150 μM.[110] Euchrestaflavanone B could inhibit the activity of protein kinase CKII with an IC_{50} 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 apoptosis-inducing effects in oral squamous cell carcinoma cells (IC_{50} 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 (IC_{50} of 18.3, 12.6, and 10.9 μM after treatment for 24, 48, and 72 h) and HNSCC12 cells (IC_{50} 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 $CHCl_3$ 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 $CHCl_3$ fraction, displayed the strongest hepatoprotective effects on tacrine-induced 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 EC_{50} 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 IC_{50} values of 9.7, 3.3, and 7.1 μM, respectively.[116] It was demonstrated that 1,1-dimethylallyl or 2,3,3-trimethyl-2,3-dihydrofuran 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 CCl_4-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-hydroxytryptamine in the central nervous system.[118] The dichloromethane (CH_2Cl_2) fraction of *C. tricuspidata* fruits was active in inhibiting mouse brain MAO, and gancaonin A (**216**),

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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 of stem bark	HL-60[a]	30 μg mL^{-1} (IC_{50})	106	The EtOAc fraction of fruits	MCF-7	66.8 μg mL^{-1} (IC_{50})	142
	U937[b]	40 μg mL^{-1} (IC_{50})	106		MDA-MB-231[f]	75.4 μg mL^{-1} (IC_{50})	142
	HeLa[c]	58 μg mL^{-1} (IC_{50})	106	Total flavonoids	BGC-823[g]	6.11 μg mL^{-1} (IC_{50})	107
	MCF-7[d]	44 μg mL^{-1} (IC_{50})	106		A549[h]	12.20 μg mL^{-1} (IC_{50})	107
	HepG2[e]	69 μg mL^{-1} (IC_{50})	106		L1210[i]	12.73 μg mL^{-1} (IC_{50})	107
Compd **1**	BGC-823	15.2 μg mL^{-1} (IC_{50})	17	Compd **72**	A549	2.8 μM (IC_{50})	49
	A549	5.93 μM (IC_{50})	49			25.8 μM (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 μM (LD_{50})	56
		43.2 μM (LD_{50})	56		HT-29	28.0 μM (LD_{50})	56
	HT-29[k]	41.4 μM (LD_{50})	56		HL-60	29.5 μM (LD_{50})	56
	HL-60	32.8 μM (LD_{50})	56		AGS	15.2 μM (LD_{50})	56
	AGS[l]	32.8 μM (LD_{50})	56	Compd **73**	HCT-116	6.66 μM (IC_{50})	55
Compd **2**	HCT-116[m]	3.9 μg mL^{-1} (IC_{50})	17		SMMC-7721	5.13 μM (IC_{50})	55
	SMMC-7721[n]	6.9 μg mL^{-1} (IC_{50})	17		SGC-7901	3.63 μM (IC_{50})	55
	SGC-7901[o]	4.3 μg mL^{-1} (IC_{50})	17		BGC-823	3.11 μM (IC_{50})	55
Compd **3**	HCT-116	12.2 μg mL^{-1} (IC_{50})	17	Compd **77**	HCT-116	2.8 μg mL^{-1} (IC_{50})	17
	SMMC-7721	8.9 μg mL^{-1} (IC_{50})	17		SMMC-7721	8.8 μg mL^{-1} (IC_{50})	17
Compd **4**	HCT-116	4.1 μg mL^{-1} (IC_{50})	17		SGC-7901	11.8 μg mL^{-1} (IC_{50})	17
	SMMC-7721	4.2 μg mL^{-1} (IC_{50})	17		BGC-823	5.2 μg mL^{-1} (IC_{50})	17
	SGC-7901	9.8 μg mL^{-1} (IC_{50})	17	Compd **78**	HCT-116	1.3 μg mL^{-1} (IC_{50})	17
Compd **5**	HCT-116	4.7 μg mL^{-1} (IC_{50})	17		SMMC-7721	6.2 μg mL^{-1} (IC_{50})	17
	SMMC-7721	4.2 μg mL^{-1} (IC_{50})	17		SGC-7901	3.4 μg mL^{-1} (IC_{50})	17
	SGC-7901	5.4 μg mL^{-1} (IC_{50})	17	Compd **84**	A549	61.9 μM (LD_{50})	56
	BGC-823	1.6 μg mL^{-1} (IC_{50})	17		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 μg mL^{-1} (IC_{50})	17		SGC-7901	28.68 μM (IC_{50})	55
	SMMC-7721	2.7 μg mL^{-1} (IC_{50})	17		BGC-823	26.90 μM (IC_{50})	55
	SGC-7901	3.4 μg mL^{-1} (IC_{50})	17		U937	6.0 μM (IC_{50})	110
	BGC-823	1.6 μg mL^{-1} (IC_{50})	17	Compd **130**	HCT-116	24.37 μM (IC_{50})	55
Compd **9**	SMMC-7721	11.7 μg mL^{-1} (IC_{50})	17		SMMC-7721	28.94 μM (IC_{50})	55
	SGC-7901	1.8 μg mL^{-1} (IC_{50})	17		SGC-7901	65.86 μM(IC_{50})	55
	BGC-823	9.2 μg 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
	SK-OV3	74.5 μM (LD_{50})	56		HeLa	0.8 μM (IC_{50})	111
	HT-29	50.7 μM (LD_{50})	56	Compd **145**	P388[p]	3.3 μg mL^{-1} (IC_{50})	30
	HL-60	40.8 μM (LD_{50})	56	Compd **149**	P388	6.2 μg 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 μg mL^{-1} (IC_{50})	30
	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		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
	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		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	28.05 μM (EC_{50})	16
	SMMC-7721	5.67 μM (IC_{50})	55		UO-31	9.78 μM (EC_{50})	16
	SGC-7901	3.07 μM (IC_{50})	55	Compd **163**	CRL1579	3.34 μM (EC_{50})	16
	BGC-823	2.82 μM (IC_{50})	55		LOX-IMVI	13.46 μM (EC_{50})	16
Compd **28**	A549	3.15 μM (IC_{50})	49		MOLT-4F	7.62 μM (EC_{50})	16
		33.5 μM (LD_{50})	56		KM12	13.84 μM (EC_{50})	16
	SK-OV3	4.72 μM (IC_{50})	49		UO-31	16.82 μM (EC_{50})	16
		38.0 μM (LD_{50})	56	Compd **164**	CRL1579	9.50 μM (EC_{50})	59
	HT-29	11.4 μM (LD_{50})	56		LOX-IMVI	16.60 μM (EC_{50})	59
	HL-60	8.6 μM (LD_{50})	56		MOLT-4F	8.90 μM (EC_{50})	59
	AGS	3.9 μM (LD_{50})	56		KM12	5.00 μM (EC_{50})	59
Compd **29**	HCT-116	3.4 μg mL^{-1} (IC_{50})	17		UO-31	5.20 μM (EC_{50})	59
	SMMC-7721	5.1 μg mL^{-1} (IC_{50})	17	Compd **165**	CRL1579	2.90 μM (EC_{50})	59

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Table 4 (*Contd.*)

Sample	Model	Active concentration	Ref.	Sample	Model	Active concentration	Ref.
	SGC-7901	9.5 μg mL^{-1} (IC_{50})	17		LOX-IMVI	12.50 μM (EC_{50})	59
	BGC-823	2.6 μg 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 μM (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 μM (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 μg mL^{-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. [i] 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 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 LPS-stimulated BV2 mouse microglia, CTXA (IC_{50} = 0.98 μM) 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 IC_{50} value of 6.28 μM and exert anti-neuroinflammatory activity by targeting iNOS and COX-2 *via* the MAPK and NF-κB pathways.[1] 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 EC_{50} 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 EC_{50} 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-κB 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.

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

Compd	EC_{50} (μM)	Ref.	Compd	EC_{50} (μM)	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

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 IC_{50} value of 9.91 μg mL^{-1} *in vitro*, and were able to reduce plasma triacylglycerol levels and delay

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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 IC_{50} 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 IC_{50} 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 dose-dependent manner, with IC_{50} 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 (PPARγ) and CCAAT/enhancer-binding protein α (C/EBPα) 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-BB-induced growth of rat aortic smooth muscle cells *via* an Akt-dependent pathway.[81] In addition, cudraflavone B was observed to inhibit the proliferation of rat aortic smooth muscle cells by inducing the expression of $p21^{cip1}$ and $p27^{kip1}$ 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).

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4.9. Antimicrobial activity

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 EC_{50} values of 803, 997, 981 and 930 μg 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 (IC_{50} = 24.4 ppm) and the *n*-BuOH fraction (IC_{50} = 88.3 ppm) of the *C. tricuspidata* stem extract could reduce the activity of tyrosinase and the melanin content in a concentration-dependent manner.[79] It was found that the flavonoids steppogenin (**149**, IC_{50} = 2.52 μM) and *trans*-dihydromorin (**160**, IC_{50} = 21.54 μM) and the phenylpropanoid oxyresveratrol (IC_{50} = 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 anti-browning 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, could induce post-transcriptional degradation of 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 IC_{50} 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-κB in RINm5F cells induced by IL-1β and IFN-γ and to inhibit the glucose-stimulated 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.[136] The anticoagulant activity of CTXA was investigated by Yoo *et al.*,[29] 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)-9*H*-xanthen-9-one, displayed nanomolar inhibitory activity (IC_{50}: 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 IC_{50} 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.

5 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. tricuspidata*-derived extracts and compounds have attracted much attention for their promising biological activities, including anti-inflammatory, antioxidant, antitumor, hepatoprotective, 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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