

REVIEW

View Article Online

View Journal | View Issue



Cite this: RSC Adv., 2017, 7, 31807

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

Lan-Ting Xin, (1) †ab Shi-Jun Yue,†ab Ya-Chu Fan,ab Jing-Shuai Wu,ab Dan Yan,c Hua-Shi Guan\*ab and Chang-Yun Wang (1) \*ab

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.

Received 17th April 2017 Accepted 3rd June 2017

DOI: 10.1039/c7ra04322h

rsc.li/rsc-advances

### 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;<sup>7</sup> 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;<sup>3</sup> 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.<sup>11</sup> Its edible fruits have been made into juices, jams, alcoholic beverages, dietary supplements and other health products in Korea.<sup>12</sup> Moreover, its bark fibers have been utilized to make paper and its trunks have been used as valuable timber for furniture manufacture.<sup>13</sup>

<sup>&</sup>lt;sup>a</sup>Key Laboratory of Marine Drugs, The Ministry of Education of China, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, P. R. China. E-mail: changyun@ouc.edu.cn; hsguan@ouc.edu.cn; Fax: +86 532 82031536; Tel: +86 532 82031536; +86 532 82031667

<sup>&</sup>lt;sup>b</sup>Laboratory for Marine Drugs and Bioproducts, Qingdao National Laboratory for Marine Science and Technology, Qingdao 266071, P. R. China

Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, P. R. China† These authors have contributed equally to this work.

**RSC Advances** Review

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).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

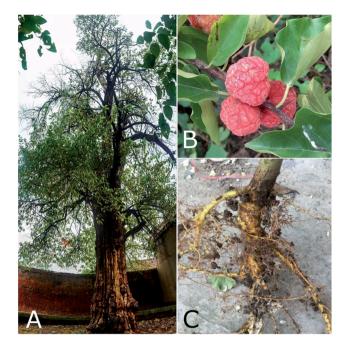


Fig. 1 Whole plant ( $\sim$ 200 years) (A), fruits (B) and roots (C) of C. tricuspidata.

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 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)

Review

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.<sup>53</sup> 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 manner<sup>54</sup> 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 Fe<sup>2+</sup> ions.<sup>56</sup>

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.<sup>57</sup> 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<sup>-1</sup> (as rutin equivalents).<sup>67</sup> 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<sup>-1</sup> in the stems, respectively.<sup>68</sup> Jeon et al.<sup>69</sup> 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  $\mu$ g g<sup>-1</sup>) 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

No.	Compound name(s)	Tissue(s)	Ref.
Kanthones	6		
1	Cudratricusxanthone A	Whole plant	49
2	Cudratricusxanthone B	Roots	17
	Cudratricusxanthone C	Roots	17
	Cudratricusxanthone D	Roots	17
;	Cudratricusxanthone E	Roots	17
<u>,</u>	Cudratricusxanthone F	Roots	17
,	Cudratricusxanthone G	Roots	17
3	Cudratricusxanthone H	Roots	17
)	Cudratricusxanthone I	Roots	55
.0	Cudratricusxanthone J	Roots	50
.1	Cudratricusxanthone K	Roots	50
.2	Cudratricusxanthone L	Roots	50
.3	Cudratricusxanthone M	Roots	50
4	Cudratricusxanthone N	Roots	143
.5	Cudratricusxanthone O	Roots	143
6	Cudratricusxanthone P/cudracuspixanthone A	Roots	116 and 143
7	Cudraxanthone A  Cudraxanthone A	Root bark	110 and 14.
8	Cudraxanthone B	Root bark	144
9	Cudraxanthone C	Root bark	144
0	Cudraxanthone D	Root bark	4
1	Cudraxanthone E	Root bark	146
2	Cudraxanthone F	Root bark	146
3	Cudraxanthone G	Root bark	146
4	Cudraxanthone H	Root bark	147
5	Cudraxanthone I	Root bark	147
6	Cudraxanthone J	Root bark	147
7	Cudraxanthone K	Root bark	147
8	Cudraxanthone L	Root bark	148
9	Cudraxanthone M	Root bark	148
0	Cudraxanthone N	Root bark	148
1	Cudraxanthone O	Root bark	148
32	Cudracuspixanthone B/cudratrixanthone B	Roots	27 and 116
3	Cudracuspixanthone C	Roots	116
4	Cudracuspixanthone D	Roots	116
5	Cudracuspixanthone E	Roots	88
6	Cudracuspixanthone F	Roots	88
7	Cudracuspixanthone G	Roots	88
8	Cudratrixanthone A	Roots Root bark	27
9	Cudratrixanthone C	Root bark	27
.0	Cudratrixanthone D	Root bark	27
1	Cudratrixanthone E	Root bark	27
2	Cudratrixanthone F	Root bark	27
3	Cudratrixanthone G	Root bark	27
4	Cudratrixanthone H	Root bark	27
5	Cudratrixanthone I	Root bark	27
6	Cudratrixanthone J	Root bark	27
7	Cudratrixanthone K	Root bark	27
8	Cudratrixanthone L	Root bark	27
9	Cudratrixanthone M	Root bark	27
0	Cudratrixanthone N	Root bark	27
1	Cudratrixanthone O	Root bark	27
2	Cudratrixanthone P	Root bark	145
3	Cudratrixanthone Q	Root bark	145
4	Cudratrixanthone R	Root bark	145
5	Cudratrixanthone S	Root bark	145
6	Cudratrixanthone T	Root bark	145
7	Cudratrixanthone U	Root bark Root bark	145
	Cudratrixanthone V		
8		Root bark	145
9	Cudratrixanthone W	Root bark	145
0	Alvaxanthone	Roots	88
1	Alloathyriol	Roots	88
52	Dulxanthone B	Twigs	75

Table 1 (Contd.)

63 64 65 66 67 68 69 70 71 72	Gerontoxanthone A Gerontoxanthone C Gerontoxanthone I Isocudraniaxanthone A Isocudraniaxanthone B	Root bark Root bark Roots	25 27
55 56 57 58 59 70 71 72	Gerontoxanthone I Isocudraniaxanthone A Isocudraniaxanthone B	Roots	
56 57 58 59 70 71 72 73	Isocudraniaxanthone A Isocudraniaxanthone B		
57 58 59 70 71 72	Isocudraniaxanthone B		88
58 59 70 71 72 73		Roots	116
59 70 71 72 73		Root bark	56
70 71 72 73	Isocudraxanthone K	Root bark	25
71 72 73	Isogentisin	Roots	88
72 73	Isoalvaxanthone	Roots	88
73	Laxanthone I	Root bark	116
	Macluraxanthone B	Whole plant	49
74	Macluraxanthone C	Roots	55
-	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
30	1,3,5-Trihydroxy-4-prenylxanthone	Roots	116
31	1,3,5-Trihydroxy-2-(3-methylbut-2-enyl)xanthone	Root bark	27
32	1,3,5,6-Tetrahydroxyxanthone	Bark	149
33	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		
34	1,3,7-Trihydroxy-4-(1,1-dimethyl-2-propenyl)-	Roots	52
	5,6-(2,2-dimethylchromeno)xanthone		
85	1,5-Dihydroxy-3,6-dimethoxyxanthen-9-one	Twigs	75
36	1,7-Dihydroxy-3,6-dimethoxyxanthone	Roots	55
37	1,6,7-Trihydroxy-2-(1,1-dimethyl-2-propenyl)-	Roots	119
	3-methoxyxanthone		
88	1,6,7-Trihydroxy-3-methyl-4-(1,1,3-trimethyl-2-	Root bark	23
	buten-1-yl)-9 <i>H</i> -xanthen-9-one		
39	2-Deprenylrheediaxanthone B	Root bark	116
90	2,6-Dihydroxyxanthone	Roots	116
91	3-O-Methylcudratrixanthone G	Root bark	27
92	5- <i>O</i> -Methylformoxanthone C	Root bark	27
93	6-Deoxyisojacareubin	Root bark	27
94	6-Deoxy-γ-mangostin	Root bark	27
95	7- <i>O</i> -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
, ,	10 Mounds dual du mandrone M	noor barn	110
Flavonoids			
Flavones			
100	Artocarpesin	Roots and stems	17
101	Apigenin	Fruits	168
102	Apigenin-7- <i>O</i> -β-p-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
100	Cudraflavone F	Roots	58
108	Cudraflavone G	Roots	58
109	Cudraflavone H	Root bark	145
109	Cycloartocarpesin B	Roots	17
110	Cyclomorusin	Twigs	75
111	Cycloartocarpin	Whole plant	75 152
	• •	whole plant Fruits	152 66
113	Hirsutrin/quercetin-3- <i>O</i> -β- <sub>D</sub> -glucopyranoside Kuwanon C	Roots	125
114			
15	Licoflavone C	Leaves	153
116 117	5,7,2',4'-Tetrahydroxyflavone/norarthocarpetin	Stems	154
	6-Prenylapigenin Kaempferol	Roots Root bark	58 134

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-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- <i>O</i> -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	(2R)-Cudraflavanone H	Root bark	145
137	(2S)-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
143	Euchrestaflavanone C	Root bark	157
145	Eriodictyol	Stem bark	30
146	Naringenin Pianana kain	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	(2S)-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- <i>O</i> -β-D-glucoside	Twigs	75
160	<i>trans</i> -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 and 100
168	Taxifolin-7-nethyl ethel Taxifolin-7-0-β-p-glucopyranoside	Twigs	
		9	75 140
169 170	Tricusposide (2 <i>S</i> ,3 <i>S</i> )-2,3- <i>trans</i> -Dihydromorin-7- <i>O</i> -β-p-glucoside	Bark	149 75
170		Twigs	
171	(2R,3R)-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

Table 1 (Contd.)

No.	Compound name(s)	Tissue(s)	Ref.
177	Cudraisoflavone E	Fruits	28
78	Cudraisoflavone F	Fruits	28
.79	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	Cudraisoflavona O	Fruits Fruits	168
190	Cudraisoflavone Q Cudraisoflavone R	Fruits	168
191	Cudraisoflavone S	Fruits	168
192	Cudraisoflavone T	Fruits	168
193	Cudracusisoflavone A	Fruits	168 66
194 195	Cudracusisoflavone B	Fruits	66
	Auriculasin	Fruits	
196 197	Anagyroidisoflavone A	Fruits	28 28
197	Alpinumisoflavone	Fruits	32
	Biochanin A	Root bark	124
199 200	Erysenegalensein E	Fruits	31
200	Isoerysenegalensein E	Fruits	31
201	Erythrinin B/wighteone/6-isopentenylgenistein	Twigs and fruits	28 and 10
202	Erythrinin C	Fruits	28 and 10.
203 204	Eryvarin B	Fruits	28
204 205	Erysubin A	Leaves	87
203 206	Euchrenone b8	Fruits	28
200 207	Euchrenone b9	Fruits	28
208	Euchrenone b10	Fruits	28
208 209	Erythrivarone A	Leaves	153
210	Derrone	Fruits	28
211	Derrone-4'-O-methyl ether	Fruits	66
211	Flaniostatin	Leaves	162
212	Flemiphilippinin B	Whole plants	163
213	Flemiphilippinin G	Fruits	28
215	Furowanin B	Leaves	86
216 216	Gancaonin A	Fruits	116
217	Gancaonin B	Fruits	28
218	Genistein	Twigs and bark	75 and 149
219	Genistein-4'- <i>O</i> -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 75
238	Ulexin B	Fruits	66
د٥٥			

Table 1 (Contd.)

No.	Compound name(s)	Tissue(s)	Ref.
240	Warangalon	Fruits	28
41	3'-O-Methylorobol	Root bark	124
42	4'-O-Methylalpinumisoflavone	Fruits and stem bark	105 and 116
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
47	5,3'-Dihydroxy-4'-methoxy-2",2"-	Fruits	31
	dimethylpyrano[5",6";6,7]isoflavone		~-
48	5,3',4'-Trihydroxy-6",6"-	Fruits	66
10	dimethylpyrano[2",3";7,6]isoflavone	Tutts	00
49	5,4'-Dihydroxy-8-(3"-methylbut-2"-enyl)-	Fruits	31
49	2"'-(4"'-hydroxy-4"'-methylethyl)furano[4"',5";6,7]isoflavone	Fluits	31
50		Emito	21
50	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
	6,8-diprenylgenistein/8- $(\gamma,\gamma$ -dimethylallyl)wighteone		
53	5,7,4'-Trihydroxydihydroisoflavone	Whole plant	152
54	6,8-Diprenylorobol/5,7,3',4'-tetrahydroxy-6,8-diprenylisoflavone	Twigs and fruits	28 and 75
55	6-Prenylorobol	Leaves	153
56	7,4'-Dimethoxy-5-hydroxyisoflavone	Fruits	66
57	8-Hydroxygenistein	Root bark	145
rganic acids		Two le	15
58 50	Butyl citrate	Trunk	15
59	Benzoic acid	Fruits	76 76
60	Boric acid	Fruits	76 <b>-</b> 0
61	Citric acid	Fruits	70
62	Mandelic acid	Fruits	76
63	Methyl linoleate	Trunk	15
64	Malic acid	Fruits	70
65	Oxalic acid	Fruits	70
66	Palmitic acid	Trunk	15
67	Palmitic acid methyl ester	Trunk	15
68	Palmitic acid β-monoglyceride	Trunk	15
69	Protocatechuic acid	Twigs	75
70	Succinic acid	Fruits	70
71	Stearic acid	Trunk	15
72	Syringic acid	Trunk	15
73	Tartaric acid	Fruits	70
74	threo-9,10-O-Isopropylidene-13-hydroxy-(11E)-octadecenoic acid	Roots	164
75	<i>n</i> -Decanoic acid	Roots and stems	10
76	n-Nonanoic acid	Roots	10
70 77	n-Pentanoic acid	Roots and stems	10
	n-Hexanoic acid	Roots and stems	
78 70			10
79 00	n-Heptanoic acid	Roots	10
80	n-Octanoic acid	Roots	10
81	(E)-2-Decenoic acid	Roots	10
32	(E)-2-Octenoic acid	Roots and stems	10
33	2',3'-Dihydroxypropyl pentadecanoate	Roots	165
34	4-Hydroxybenzoic acid	Fruits	168
35	9,12-Octadecadienoic acid	Trunk	15
36	9,12,15-Octadecatrienoic acid methyl ester	Trunk	15
87	9,12,15-Octadecatrien-1-ol	Trunk	15
88	9,17-Octadecadienal	Trunk	15
89	γ-Hexadecalactone	Root bark	145
1 1	1		
olysaccharid	les CTP-B1	Roots	73

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
95	CTPS-3A	Roots	71
henylpro	ppanoids		
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
806	Oxyresveratrol	Twigs	75
307	Scopoletin	Trunk	15
808	Schizandrin	Whole plant	166
809	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
313	5-Methoxy-4,5-diphenyl-2(5 <i>H</i> )-furanone	Twigs	75
14	3-Methyl-2(5 <i>H</i> )-furanone	Roots	10
15	5-Ethyl-2(5 <i>H</i> )-furanone	Roots	10
16	5,5-Dimethyl- $2(5H)$ -furanone	Roots	10
Other ing	redients		
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- <i>O</i> -acetate	Whole plant	152
328	Olean-12-ene	Trunk	15
329	Taraxerone	Stems	160
330	Terpin hydrate	Roots	10
31	Ursolic acid	Roots	165
332	(E)-Geranylacetone	Roots	10
33	(E)-\text{\text{\$\text{\$F\$-Ionone}}}	Roots and stems	10
34	(E)-Linalool oxide	Roots	10
35	(Z)-Linalool oxide	Roots	10
336	$(E)$ - $\alpha$ -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 Whole plant	15 162
343	Achilleol A	Whole plant	163 76
344	Antiarol	Fruits	76 10
345	Anisaldehyde	Roots	10
346	Aristolone	Trunk	15 76
347	Adacene 12 Brosimine B	Fruits Root bark	76 145
10		ROOL DALK	145
348 349	Benzophenone	Stems	10

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
53	Cudracuspiphenone A	Roots	116
54	Cudracuspiphenone B	Roots	116
555	Cudrachromone A	Root bark	145
556	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
861	Cudrabibenzyl A	Fruits	168
62	(E)-Cinnamic aldehyde	Roots and stems	10
363	Dopamine	Fruits	76
664	Demeton-O-methyl	Fruits	76
65	Diethyl phthalate	Fruits	76
666	Ethyl- <i>N</i> -methylcarbamate	Fruits	76
67	Eriosematin A	Root bark	145
68	Ethyl <i>p-tert</i> -butylbenzoic acid	Fruits	76
669	Eugenol	Roots and stems	10
570	Isoeugenol	Roots	10
870 871	Isoengenoi	Roots Root bark	10 145
	Indene	Fruits	76
372			
373	Lavender lactone	Roots	10
374	Lycopene	Fruits	77 
375	Lutein	Fruits	77 76
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
881	Pyridine	Roots	10
382	Pyrrole-2-carboxaldehyde	Stems	10
883	Ruboxanthin	Fruits	77
884	Salicylamide	Fruits	76
885	Scyllitol	Fruits	76
886	Sucrose	Bark	149
887	Stachydrine	Roots	167
888	Tridecanol	Fruits	76
889	Undecane	Fruits	76
90	Vanillin	Root bark	145
91	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
896	<i>n</i> -Nonanal	Roots and stems	10
97	<i>N</i> -Acetylnorephedrine	Fruits	76
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 76
02	2-Deuteriophenylalanine	Fruits	76 76
103	2-Furanmethanol	Trunk	15
03	2-Ethyl-1-hexanol	Roots and stems	10
	2-Ethyl-1-nexanor 2-Acetylpyrrole	Stems	10
.05			
.06	2,3-Dihydro-3,5-dihydroxy-6-methyl-4 <i>H</i> -pyran-4-one	Trunk	15
107	2,4-Bis(4-hydroxybenzyl)phenol	Root bark and stems	10 and 14
.08	2,5-Furandione	Trunk	15
109	3-Methoxycarbonylindole	Root bark	145
10	3-Methyl-2,5-furandione	Trunk	15
11	4-Acetylpyrazole	Roots	10
112	4-Ethylguaiacol 4-Hydroxybenzalacetone	Roots and stems	10

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 1		
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  $\alpha$ -D-glucuronic acid, 4-*O*-methyl- $\alpha$ -D-glucuronic acid, and neutral sugar units such as  $\alpha$ -L-arabinose,  $\alpha$ -D-xylose and  $\alpha$ -D-galactose. A

### 3.5. Phenylpropanoids (296–316)

Twenty-one phenylpropanoids have been reported in *C. tricus- pidata*, such as oxyresveratrol (306),<sup>75</sup> scopoletin (307),<sup>15</sup> 3-methyl-2(5*H*)-furanone (314),<sup>10</sup> and 5-ethyl-2(5*H*)-furanone (315).<sup>10</sup> 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.<sup>75</sup>

### 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).<sup>76</sup> 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),  $\alpha$ -carotene (428),  $\beta$ -carotene (429), neo- $\beta$ -carotene (430) and polycopene (443).<sup>77</sup>

### 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,<sup>22,23</sup> antioxidant,<sup>78,79</sup> antitumor,<sup>16,24</sup> hepatoprotective,<sup>25,26</sup> neuroprotective,<sup>27,28</sup> antiobesity,<sup>18,19</sup> immunomodulatory,<sup>70,71</sup> anti-atherosclerotic,<sup>80,81</sup> antimicrobial,<sup>11,76</sup> skin-protecting,<sup>79,82</sup> and antidiabetic<sup>21,52</sup> 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-

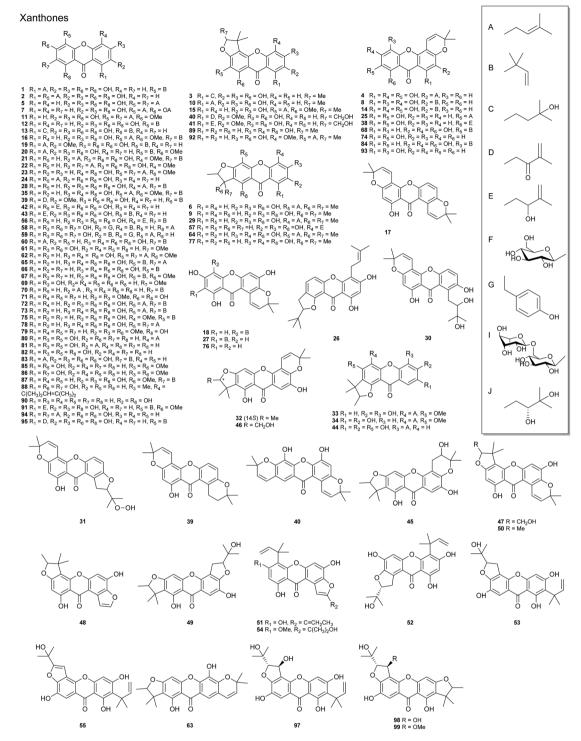


Fig. 2 Chemical structures of xanthones and flavonoids isolated from C. tricuspidata.

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- $\gamma$  (IFN- $\gamma$ ) 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  $E_2$  (PGE<sub>2</sub>) by decreasing the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) and reducing the levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-1 $\beta$  and IL-6 in RAW 264.7 mouse macrophage cells stimulated with lipopolysaccharide (LPS).<sup>83</sup> The ethyl acetate (EtOAc) fraction of the stem bark could

Review

# **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-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<sub>2</sub> 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 antiinflammatory 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 μM, respectively.87 It was found that the position of hydroxyl groups in the xanthone moiety was important for the NOinhibiting 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

Fig. 2 (contd.)

via the regulation of NF-κB in LPS-stimulated RAW 264.7 cells.<sup>34</sup> The xanthone CTXA, as an effective inducer of heme oxygenase-1 (HO-1), significantly inhibited the production of PGE<sub>2</sub>, NO, TNF- $\alpha$ , and IL-1 $\beta$  and increased the activity of HO in LPSstimulated RAW 264.7 macrophages.<sup>22</sup> Moreover, CTXA could exert anti-soluble endothelial cell protein C receptor (antisEPCR) shedding activity against vascular inflammation via inhibiting the expression of TNF- $\alpha$ -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 (FcεRI) and the expression of FcεRIβ mRNA but also inhibited the redistribution of F-actin and downstream signalling by suppressing the activation of FceRImediated 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- $\gamma$ , and IL-1 $\beta$ ), which are indirectly activated by bisphenol A or di(2-ethylhexyl) phthalate in HMC-1 and RBL-2H3 cells. 33,92-96

Review

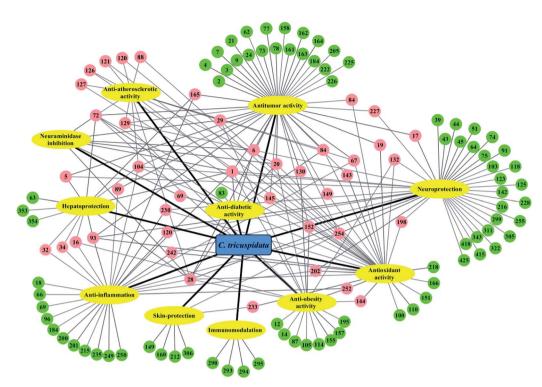


Fig. 3 Pharmacological activities of 124 active components from C. tricuspidata. The active compounds (circles) map ten pharmacological properties (yellow ovals). The pink circles represent multiple pharmacological properties. The green circles represent only one pharmacological property.

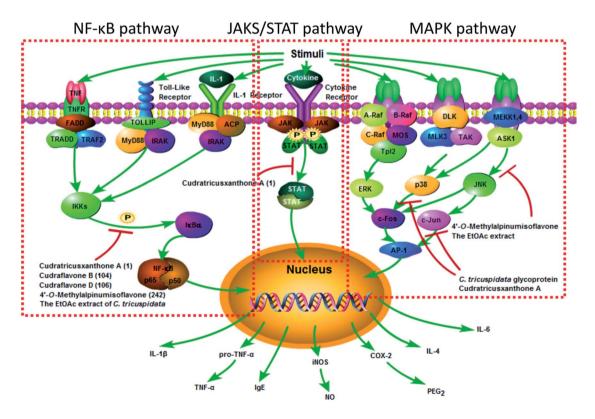


Fig. 4 Molecular mechanisms of anti-inflammatory extracts and compounds from C. tricuspidata.

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<sup>-1</sup>), in particular quercetin.<sup>97,98</sup> 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<sup>-1</sup>) 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<sup>-1</sup>) exhibited strong scavenging activities against DPPH, superoxide anions and hydroxyl radicals, with no pro-oxidant activity in vitro.<sup>34</sup> 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.<sup>7,55</sup> An EtOAc extract of

 Table 3
 Antioxidant activities of extracts and compounds of C. tricuspidata<sup>a</sup>

	$IC_{50}$			
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	$54.48 \text{ mg mL}^{-1}$	N.A	$15.13 \text{ mg mL}^{-1}$	156
The ethyl ether fraction of MeOH extract of root bark	$30.78 \text{ mg mL}^{-1}$	N.A	$7.72 \text{ mg mL}^{-1}$	156
The EtOAc fraction of MeOH extract of root bark	$20.32 \text{ mg mL}^{-1}$	N.A	$7.46 \text{ mg mL}^{-1}$	156
The <i>n</i> -BuOH fraction of MeOH extract of root bark	$93.37 \text{ mg mL}^{-1}$	N.A	>20 mg mL <sup>-1</sup>	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 <b>120</b>	$4.14~\mu\mathrm{g~mL}^{-1}$	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 <b>M</b>	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 <b>M</b>	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.

Review RSC Advances

*C. tricuspidata* stem bark displayed significant cytotoxicity against HL-60 cells, and the mechanism underlying its cytotoxicity may be due to apoptosis. <sup>106</sup> A CHCl<sub>3</sub> extract of *C. tricuspidata* roots exhibited significant cytotoxicity against human gastric carcinoma cell lines (SGC-7901 and BGC-823). <sup>17</sup> 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. <sup>107</sup> In nude mouse models of B16 melanoma and human SK-OV3 xenografted tumors, the tumor-inhibiting rates of the total flavonoids (250 mg kg<sup>-1</sup>) from *C. tricuspidata* were 50.54% and 46.38%, respectively. <sup>108</sup>

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.<sup>56</sup> 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 IC<sub>50</sub> of 0.4 mM and inhibited the activity of protein kinase C with an IC<sub>50</sub> of 150 μM.<sup>110</sup> 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  $\mu M$  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.<sup>24</sup> 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.<sup>115</sup> 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<sup>-1</sup>.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 IC<sub>50</sub> 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.<sup>117</sup> CTXA and cudraflavone B displayed significant neuroprotective activity against glutamate-induced neurotoxicity *via* the induction of HO-1 in HT22 mouse hippocampal cells.<sup>51,62</sup> The neuroprotective effect of cudraflavone B was probably regulated by the phosphatidylinositol 3-kinase (PI3K)/AKT pathways.<sup>62</sup>

MAOs are responsible for the degradation of neurotransmitters including noradrenaline, dopamine, and 5-hydroxy-tryptamine in the central nervous system. The dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>) 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

Open Access Article. Published on 22 2017. Downloaded on 30.10.2025 22:53:26.

This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Sample Model Active concentration Sample Model Active concentration Ref. Ref.  $30 \ \mu g \ mL^{-1} \left(IC_{50}\right)$ The EtOAc fraction The EtOAc extract HL-60a 106 MCF-7 66.8  $\mu g \text{ mL}^{-1} (IC_{50})$ 142  $U937^b$  $40 \ \mu g \ mL^{-1} (IC_{50})$ MDA-MB-231<sup>f</sup> 75.4  $\mu g \text{ mL}^{-1} (IC_{50})$ of stem bark 106 of fruits 142  $58 \, \mu \text{g mL}^{-1} \, (\text{IC}_{50})$ 6.11  $\mu g \text{ mL}^{-1} (IC_{50})$  $HeLa^c$ 106 Total flavonoids BGC-823g 107  $MCF-7^d$  $44 \mu g \text{ mL}^{-1} (IC_{50})$ 12.20  $\mu g \text{ mL}^{-1} (IC_{50})$ A549<sup>h</sup> 106 107 69  $\mu g \text{ mL}^{-1} (IC_{50})$ 12.73 μg mL<sup>-1</sup> (IC<sub>50</sub>) HepG2<sup>e</sup> 106  $L1210^i$ 107 Compd 1 Compd 72 BGC-823 15.2  $\mu g \text{ mL}^{-1} (IC_{50})$ 17 A549 2.8 µM (IC<sub>50</sub>) 49 25.8 μM (LD<sub>50</sub>) A549 5.93 µM (IC<sub>50</sub>) 49 56 45.8 μM (LD<sub>50</sub>) 4.24 μM (IC<sub>50</sub>) SK-OV3 49 56 SK-OV3<sup>j</sup> 7.09 µM (IC<sub>50</sub>) 49 23.1 µM (LD<sub>50</sub>) 56 43.2 μM (LD<sub>50</sub>) HT-29 28.0 μM (LD<sub>50</sub>) 56 56  $\text{HT-29}^k$ 41.4 µM (LD<sub>50</sub>) 56 HL-60 29.5 µM (LD<sub>50</sub>) 56 HL-60 32.8 μM (LD<sub>50</sub>) 56 AGS 15.2 μM (LD<sub>50</sub>) 56  $AGS^{l}$ 32.8 µM (LD<sub>50</sub>) 56 Compd 73 HCT-116 6.66 µM (IC<sub>50</sub>) 55 HCT-116<sup>m</sup>  $3.9 \ \mu g \ mL^{-1} (IC_{50})$ Compd 2 17 SMMC-7721 5.13 μM (IC<sub>50</sub>) 55 6.9  $\mu g \text{ mL}^{-1} (IC_{50})$ SMMC-7721<sup>n</sup> 17 SGC-7901 3.63 µM (IC<sub>50</sub>) 55 4.3  $\mu g \text{ mL}^{-1} (IC_{50})$ SGC-7901° 17 **BGC-823**  $3.11 \mu M (IC_{50})$ 55 12.2  $\mu g \text{ mL}^{-1} (IC_{50})$ Compd 3 HCT-116 17 Compd 77 HCT-116  $2.8 \ \mu g \ mL^{-1} (IC_{50})$ 17 8.8  $\mu g \text{ mL}^{-1} (IC_{50})$ SMMC-7721 8.9  $\mu g \text{ mL}^{-1} (IC_{50})$ 17 SMMC-7721 17 4.1  $\mu g \ mL^{-1} \left(IC_{50}\right)$ Compd 4 HCT-116 17 SGC-7901 11.8  $\mu g \text{ mL}^{-1} (IC_{50})$ 17 4.2  $\mu g \text{ mL}^{-1} (IC_{50})$ 17 BGC-823  $5.2 \ \mu g \ mL^{-1} (IC_{50})$ 17 SMMC-7721 SGC-7901 9.8 μg mL  $(IC_{50})$ 17 Compd 78 HCT-116 1.3  $\mu g \text{ mL}^{-1} (IC_{50})$ 17 Compd 5 17 6.2  $\mu g \text{ mL}^{-1} (IC_{50})$ HCT-116  $4.7 \ \mu g \ mL^{-1}$ (IC50) SMMC-7721 17  $4.2~\mu g~mL^{-1}$  $3.4 \ \mu g \ mL^{-1} (IC_{50})$ SMMC-7721 17 SGC-7901 17  $(IC_{50})$  $5.4 \, \mu \text{g mL}^{-1} \, (\text{IC}_{50})$ SGC-7901 17 Compd 84 A549 61.9 µM (LD<sub>50</sub>) 56 1.6  $\mu g \text{ mL}^{-1} (IC_{50})$ BGC-823 17 SK-OV3 70.4 µM (LD<sub>50</sub>) 56  $21.31~\mu M~(IC_{50})$ Compd 6 HT-29 46.3 μM (LD<sub>50</sub>) HCT-116 55 56  $50.7 \mu M (IC_{50})$ SMMC-7721 55 HL-60 35.9 μM (LD<sub>50</sub>) 56 SGC-7901 26.34 µM (IC<sub>50</sub>) 44.7 μM (LD<sub>50</sub>) 55 AGS 56 32.04 µM (IC<sub>50</sub>) BGC-823 17.62 μM (IC<sub>50</sub>) 55 Compd 129 SMMC-7721 55 Compd 7 HCT-116 1.8  $\mu g \text{ mL}^{-1} (IC_{50})$ 17 SGC-7901 28.68 µM (IC<sub>50</sub>) 55  $2.7 \ \mu g \ mL^{-1} \left(IC_{50}\right)$ SMMC-7721 26.90 μM (IC<sub>50</sub>) 17 **BGC-823** 55  $3.4 \ \mu g \ mL^{-1} \ (IC_{50})$ SGC-7901 17 U937 6.0 µM (IC50) 110 1.6  $\mu g \text{ mL}^{-1} (IC_{50})$ 24.37 μM (IC<sub>50</sub>) BGC-823 17 Compd 130 HCT-116 55 11.7  $\mu g \text{ mL}^{-1} (IC_{50})$ Compd 9 17 SMMC-7721 SMMC-7721 28.94 µM (IC<sub>50</sub>) 55 1.8  $\mu g \text{ mL}^{-1} (IC_{50})$ SGC-7901 17 SGC-7901 65.86  $\mu$ M(IC<sub>50</sub>) 55 9.2  $\mu g \text{ mL}^{-1} (IC_{50})$ BGC-823 17 BGC-823 28.68 μM (IC<sub>50</sub>) 55 Compd 19 61.7 μM (LD<sub>50</sub>) Compd 143 U937 0.8 μM (IC<sub>50</sub>) A549 56 111 SK-OV3 74.5  $\mu$ M (LD<sub>50</sub>) 56 HeLa  $0.8 \, \mu M \, (IC_{50})$ 111 50.7 μM (LD<sub>50</sub>) HT-29 56 Compd 145 P388<sup>F</sup> 3.3  $\mu g \text{ mL}^{-1} (IC_{50})$ 30 6.2  $\mu g \text{ mL}^{-1} (IC_{50})$ Compd 149 HL-60 40.8 μM (LD<sub>50</sub>) 56 P388 30 10.0 μM (IC<sub>50</sub>) AGS 49.5 μM (LD<sub>50</sub>) 56 Compd 152 U937 109 Compd 20 A549 16.3 μM (LD<sub>50</sub>) 56 Compd 158 P388 15.0  $\mu g \text{ mL}^{-1} (IC_{50})$ 30 23.8  $\mu$ M (LD<sub>50</sub>)  $\mathrm{CRL1579}^q$ SK-OV3 56 Compd 161 3.65 µM (EC50) 16 HT-29 20.7 μM (LD<sub>50</sub>) 56 LOX-IMVI 11.99 µM (EC50) 16 HL-60 6.2 µM (LD<sub>50</sub>) 56 MOLT-4F<sup>s</sup> 2.65 µM (EC<sub>50</sub>) 16 AGS 4.7 μM (LD<sub>50</sub>) 56 KM12 13.70 µM (EC50) 16 Compd 21 HCT-116 26.05 μM (IC<sub>50</sub>) 55  $\text{UO-}31^u$ 6.99 µM (EC<sub>50</sub>) 16 SMMC-7721 38.32 µM (IC<sub>50</sub>) 55 Compd 162 CRL1579 13.12 µM (EC<sub>50</sub>) 16 SGC-7901 32.04 μM (IC<sub>50</sub>) 55 LOX-IMVI 31.26 µM (EC<sub>50</sub>) 16 BGC-823 40.24 μM (IC<sub>50</sub>) 55 MOLT-4F 23.07 μM (EC<sub>50</sub>) 16 5.50 μM (IC<sub>50</sub>) 28.05 μM (EC<sub>50</sub>) Compd 24 HCT-116 55 KM12 16 SMMC-7721 5.67 μM (IC<sub>50</sub>) 55 UO-31 9.78 µM (EC<sub>50</sub>) 16 SGC-7901 3.07 µM (IC<sub>50</sub>) Compd 163 CRL1579 3.34 µM (EC<sub>50</sub>) 16 55 BGC-823  $2.82 \mu M (IC_{50})$ 55 LOX-IMVI 13.46 µM (EC<sub>50</sub>) 16 Compd 28 A549 49 MOLT-4F 7.62 µM (EC<sub>50</sub>) 16  $3.15 \mu M (IC_{50})$ 

Compd 29

SK-OV3

HT-29

HL-60

HCT-116

SMMC-7721

AGS

33.5  $\mu$ M (LD<sub>50</sub>)

4.72 μM (IC<sub>50</sub>)

38.0 µM (LD<sub>50</sub>)

11.4 µM (LD<sub>50</sub>)

8.6 μM (LD<sub>50</sub>)

3.9  $\mu$ M (LD<sub>50</sub>)

 $3.4 \ \mu g \ mL^{-1} (IC_{50})$ 

 $5.1 \ \mu g \ mL^{-1} \left(IC_{50}\right)$ 

56

49

56

56

56

56

17

17

Compd 164

Compd 165

13.84 µM (EC50)

16.82 μM (EC<sub>50</sub>)

16.60 µM (EC50)

 $9.50 \mu M (EC_{50})$ 

8.90 μM (EC<sub>50</sub>)

5.00 μM (EC<sub>50</sub>)

5.20 µM (EC<sub>50</sub>)

2.90 µM (EC<sub>50</sub>)

16

16

59

59

59

59

59

59

KM12

UO-31

KM12

UO-31

CRL1579

LOX-IMVI

MOLT-4F

CRL1579

Table 4 (Contd.)

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

<sup>&</sup>lt;sup>a</sup> HL-60 = promyelocytic leukemia cell line. <sup>b</sup> U937 = human leukemia cell line. <sup>c</sup> HeLa = human carcinoma cell line. <sup>d</sup> MCF-7 = human breast cancer cell line. <sup>e</sup> HepG2 = human hepatoma cell line. <sup>f</sup> MDA-MB-231 = human breast cancer cell line. <sup>g</sup> BGC-823 = stomach cancer cell line. <sup>h</sup> A549 = lung carcinoma cell line. <sup>l</sup> L1210 = mouse leukemia cell line. <sup>j</sup> SK-OV3 = human ovarian cancer cell line. <sup>k</sup> HT-29 = human colon carcinoma cell line. <sup>l</sup> AGS = human lung cancer cell line. <sup>m</sup> HCT-116 = human colon carcinoma cell line. <sup>n</sup> SMMC-7721 = human hepatocellular carcinoma cell line. <sup>o</sup> SGC-7901 = human gastric cancer cell line. <sup>p</sup> P388 = mouse leukemia cell line. <sup>q</sup> CRL1579 = human skin cancer cell line. <sup>r</sup> LOX-IMVI = human melanoma cell line. <sup>s</sup> MOLT-4F = human leukemia cell line. <sup>t</sup> KM12 = human colon carcinoma cell line. <sup>u</sup> 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). <sup>118</sup> 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. <sup>50</sup>

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  $\alpha$ -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 EC<sub>50</sub> 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<sub>50</sub> value of 0.17 μM.<sup>122</sup> 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 IC $_{50}$  value of 9.91  $\mu$ 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.<sup>12</sup> Flavonoids isolated from C. tricuspidata, namely, cudraflavanones A and D and 5,7,4'-trihydroxy-6,8-diprenylisoflavone, inhibited PL, with IC<sub>50</sub> 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<sub>50</sub> value of 16.8  $\mu M$ , 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 IC<sub>50</sub> values ranging from 1.9 to 13.6 μM.<sup>125</sup> 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  $\gamma$  (PPAR $\gamma$ ) and CCAAT/enhancer-binding protein  $\alpha$  (C/EBP $\alpha$ ) 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<sup>-1</sup>, 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

Review

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<sup>-1</sup> and 500-1000 μg mL<sup>-1</sup>, respectively.<sup>76</sup> 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<sub>50</sub> 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.<sup>131</sup> 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.<sup>131</sup> 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.<sup>132</sup> 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<sub>50</sub> = 24.4 ppm) and the *n*-BuOH fraction (IC<sub>50</sub> = 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  $\mu$ M) and the phenylpropanoid oxyresveratrol (IC<sub>50</sub> = 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.<sup>75</sup> 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.<sup>32</sup> 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<sup>-1</sup>, 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<sub>50</sub> values of 16.2-52.9 μM.<sup>52</sup> 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.*<sup>53</sup> 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 (IC<sub>50</sub>: 80–270 nM) against neuraminidase. Cudraflavanone A, which bears a C-8 hydrated prenyl group,

**RSC Advances** Review

also displayed high neuraminidase-inhibiting activity, with an IC<sub>50</sub> of 380 nM.<sup>137</sup> 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.

# Acknowledgements

We would like to thank Drs Xue-qing Zhang (Ocean University of China), Cheng Qu (Nanjing University of Chinese Medicine) and master Miao-yin Zhang (The Johns Hopkins University) for critically reading a previous version of this manuscript. We apologize to authors whose relevant work was not included in this review owing to space constraints. This work was supported by the National High Technology Research and Development Program of China (863 Program) (No. 2013AA093001), The Scientific and Technological Innovation Project Financially Supported by Qingdao National Laboratory for Marine Science and Technology (No. 2015ASKJ02), and the Taishan Scholars Program, China.

### Notes and references

- 1 D. C. Kim, C. S. Yoon, T. H. Quang, W. Ko, J. S. Kim, H. Oh and Y. C. Kim, Int. J. Mol. Sci., 2016, 17, 255.
- 2 B. S. Jung and M. K. Shin, Encyclopedia of Illustrated Korean Natural Drugs, Young Lim Press, Seoul, 1990.
- 3 L. Reich, Uncommon Fruits for Every Garden, Timber Press, Portland, 2004.

Review

- 4 T. Fujimoto, Y. Hano and T. Nomura, *Planta Med.*, 1984, **50**, 218–221.
- 5 Chinese Pharmacopoeia Commission, *Pharmacopoeia of the People's Republic of China*, China Medical Science and Technology Press, Beijing, 1997, vol. I, p. 467.
- 6 Nanjing University of Traditional Chinese Medicine, Dictionary of Chinese Herbal Medicine, Science and Technology Press, Shanghai, 2006.
- 7 Jiangsu New Medical College, *Encyclopedia of Chinese Medicinal Substances*, Shanghai People's Publisher, Shanghai, China, 1977.
- 8 H. H. Ding, D. H. Chen, L. F. Zhu, Q. Wu and X. H. Zhou, *Zhongchengyao*, 2001, **23**, 151–152.
- 9 T. J. Kim, H. J. Han, Y. Lim, M. C. Song, J. Kim, J. T. Hong, H. S. Yoo, M. Y. Pyo, B. Y. Hwang, M. K. Lee and Y. P. Yun, *J. Cardiovasc. Pharmacol.*, 2009, **53**, 341–348.
- 10 S. Nam, H. W. Jang and T. Shibamoto, *J. Agric. Food Chem.*, 2012, **60**, 9097–9105.
- 11 Y. Z. Yu, Y. C. Deng, X. Qin, M. Zhang, L. F. Li and Z. W. Kong, *Agrochemicals*, 2009, 48, 224–226.
- 12 J. Y. Jeong, Y. H. Jo, K. Y. Lee, S. Do, B. Y. Hwang and M. K. Lee, *Bioorg. Med. Chem. Lett.*, 2014, 24, 2329–2333.
- 13 Y. T. Hou, Tezhong Jingji Dongzhiwu, 2001, 7, 25.
- 14 O. K. Kim, D. E. Nam, W. J. Jun and J. M. Lee, *J. Food Biochem.*, 2015, **39**, 508–516.
- S. H. Chang, E. J. Jung, D. G. Lim, B. Oyungerel, K. II Lim,
   E. Her, W. S. Choi, M. H. Jun, K. D. Choi, D. J. Han and
   S. C. Kim, *J. Pharm. Pharmacol.*, 2008, 60, 1221–1226.
- 16 I. K. Lee, C. J. Kim, K. S. Song, H. M. Kim, H. Koshino, M. Uramoto and I. D. Yoo, *Phytochemistry*, 1996, 41, 213– 216.
- 17 Y. S. Zou, A. J. Hou, G. F. Zhu, Y. F. Chen, H. D. Sun and Q. S. Zhao, *Bioorg. Med. Chem.*, 2004, **12**, 1947–1953.
- 18 Y. S. Kim, Y. Lee, J. Kim, E. Sohn, C. S. Kim, Y. M. Lee, K. Jo, S. Shin, Y. Song, J. H. Kim and J. S. Kim, *J. Evidence-Based Complementary Altern. Med.*, 2012, 277–293.
- 19 D. H. Kim, S. Lee, Y. W. Chung, B. M. Kim, H. Kim, K. Kim and K. M. Yang, *BioMed Res. Int.*, 2016, 2016, 8432759.
- 20 O. K. Kim, D. E. Nam, W. J. Jun and J. M. Lee, *Food Nutr. Res.*, 2015, **59**, 29165.
- 21 H. U. Son and S. H. Lee, Biomed. Rep., 2013, 1, 624-628.
- 22 G. S. Jeong, D. S. Lee and Y. C. Kim, *Int. Immunopharmacol.*, 2009, **9**, 241–246.
- 23 K. H. Park, Y. D. Park, J. M. Han, K. R. Im, B. W. Lee, Y. Jeong, T. S. Jeong and W. S. Lee, *Bioorg. Med. Chem. Lett.*, 2006, 16, 5580–5583.
- 24 L. Kuang, L. Wang, Q. Wang, Q. Zhao, B. Du, D. Li, J. Luo, M. Y. Liu, A. J. Hou and M. Qian, *Biochem. Pharmacol.*, 2011, 81, 1192–1200.
- 25 R. B. An, D. H. Sohn and Y. C. Kim, *Biol. Pharm. Bull.*, 2006, **29**, 838–840.
- 26 Y. H. Tian, H. C. Kim, J. M. Cui and Y. C. Kim, *Arch. Pharm. Res.*, 2005, **28**, 44–48.
- 27 J. Kwon, N. T. Hiep, D. W. Kim, B. Y. Hwang, H. J. Lee, W. Mar and D. Lee, *J. Nat. Prod.*, 2014, 77, 1893–1901.
- 28 N. T. Hiep, J. Kwon, D. W. Kim, B. Y. Hwang, H. J. Lee, W. Mar and D. Lee, *Phytochemistry*, 2015, **111**, 141–148.

- 29 H. Yoo, S. K. Ku, W. Lee, S. Kwak, Y. D. Baek, B. W. Min, G. S. Jeong and J. S. Bae, *Arch. Pharmacal Res.*, 2014, 37, 1069–1078.
- 30 I. K. Lee, K. S. Song, C. J. Kim, H. M. Kim, G. T. Oh and I. D. Yoo, *Agric. Chem. Biotechnol.*, 1994, 37, 105–109.
- 31 X. H. Han, S. S. Hong, Q. Jin, D. Lee, H. K. Kim, J. Lee, S. H. Kwon, D. Lee, C. K. Lee, M. K. Lee and B. Y. Hwang, *J. Nat. Prod.*, 2009, 72, 164–167.
- 32 G. M. Uddin, H. J. Lee, J. S. Jeon, D. Chung and Y. C. Kim, *Nat. Prod. Sci.*, 2011, **17**, 206–211.
- 33 J. Lee, S. J. Lee and K. T. Lim, Food Chem. Toxicol., 2012, 50, 2109–2117.
- 34 H. Y. Joo and K. T. Lim, Environ. Toxicol. Pharmacol., 2009, 27, 247–252.
- 35 H. Y. Joo and K. T. Lim, *Korean J. Food Sci. Technol.*, 2009, **41**, 93–99.
- 36 P. S. Oh and K. T. Lim, J. Appl. Toxicol., 2009, 29, 496-504.
- 37 Editorial Board of Flora of China, *Flora of China*, Science Publishing House, Beijing, 2003, vol. 5, pp. 35–36.
- 38 W. Y. Xiong, J. Z. Wang and T. D. Shi, *Woody Medicine Plants of China*, Shanghai: Shanghai Science and Education Press, Shanghai, 1993, pp. 85–88.
- 39 L. Shi, Asian J. Exp. Biol. Sci., 2010, 1, 311-314.
- 40 M. Aleksandar, Journal of Mountain Agriculture on the Balkans, 2016, 19, 134-147.
- 41 H. J. Choi, C. T. Kim, Y. D. Min and M. J. Rang, *J. Med. Plants Res.*, 2013, 14, 7–14.
- 42 Z. Q. Chen, *Ben Cao Shi Yi*, People's Medical Publishing House, Beijing, 1994, vol. II.
- 43 Z. S. Kou, *Ben Cao Yan Yi*, China Medical Science Press, Beijing, 2005.
- 44 Z. M. Mi, *Ben Cao Hui Yan*, Shanghai Science & Technology Publishing House Press, Shanghai, 2005, p. 630.
- 45 B. D. Xiao, *Lingnan Caiyao Lu*, Guangdong Science Publishing House Press, Guangdong, 2009.
- 46 N. H. Li, *Chinese Medicinal Herbs of Hong Kong*, The Commercial Press, Hong Kong, 2002.
- 47 H. S. Guan and S. G. Wang, *Chinese Marine Materia Medica*, Science and Technology Press, Shanghai, China, 2009, p. 371.
- 48 Donguibogam Committee, *Translated Donguibogam*, Bubinmunwha Press, Seoul, 1999.
- 49 B. W. Lee, S. W. Gal, K. M. Park and K. H. Park, *J. Nat. Prod.*, 2005, **68**, 456–458.
- 50 J. H. Hwang, S. S. Hong, X. H. Han, J. S. Hwang, D. Lee, H. Lee, Y. P. Yun, Y. Kim, J. S. Ro and B. Y. Hwang, *J. Nat. Prod.*, 2007, 70, 1207–1209.
- 51 G. S. Jeong, R. B. An, H. O. Pae, H. T. Chung, K. H. Yoon, D. G. Kang, H. S. Lee and Y. C. Kim, *Planta Med.*, 2008, 74, 1368–1373.
- 52 E. J. Seo, M. J. Curtis-Long, B. W. Lee, H. Y. Kim, Y. B. Ryu, T. Jeong, W. S. Lee and K. H. Park, *Bioorg. Med. Chem. Lett.*, 2007, 17, 6421–6424.
- 53 Y. B. Ryu, M. J. Curtis-Long, J. W. Lee, J. H. Kim, J. Y. Kim, K. Y. Kang, W. S. Lee and K. H. Park, *Bioorg. Med. Chem.*, 2009, 17, 2744–2750.
- 54 P. J. O'Brien, Chem.-Biol. Interact., 1991, 80, 1-41.

- 55 Y. S. Zou, A. J. Hou and G. F. Zhu, Chem. Biodiversity, 2005, 2, 131-138.
- 56 B. W. Lee, J. H. Lee, S. T. Lee, H. S. Lee, W. S. Lee, T. S. Jeong and K. H. Park, Bioorg. Med. Chem. Lett., 2005, 15, 5548-
- 57 M. B. Wang, J. M. Huang and A. J. Hou, Fudan University Journal of Medical Sciences, 2006, 33, 559-562.
- 58 L. Chen, Y. Duan, C. Li, Y. Wang, X. Tong, Y. Dai and X. Yao, Magn. Reson. Chem., 2013, 51, 842-846.
- 59 I. K. Lee, C. J. Kim, K. S. Song, H. M. Kim, I. D. Yoo, H. Koshino, Y. Esumi and M. Uramoto, J. Nat. Prod., 1995, 58, 1614-1617.
- 60 J. Hošek, M. Bartos, S. Chudík, S. Dall'Acqua, G. Innocenti, M. Kartal, L. Kokoška, P. Kollăr, Z. Kutil, P. Landa, R. Marek, V. Závalová, M. Žemlička and K. Šmejkal, J. Nat. Prod., 2011, 74, 614-619.
- 61 H. J. Lee, Q. S. Auh, Y. M. Lee, S. K. Kang, S. W. Chang, D. S. Lee, Y. C. Kim and E. C. Kim, *Planta Med.*, 2013, 79, 1298-1306.
- 62 D. S. Lee, W. Ko, D. C. Kim, Y. C. Kim and G. S. Jeong, Molecules, 2014, 19, 10818-10831.
- 63 B. W. Lee, N. S. Kang and K. H. Park, J. Korean Soc. Appl. Biol. Chem., 2004, 47, 270-273.
- 64 Y. Z. Yin, R. D. Chen, D. W. Zhang, L. R. Qiao, J. H. Li, R. S. Wang, X. Liu, L. Yang, D. Xie, J. H. Zou, C. M. Wang and J. G. Dai, J. Mol. Catal. B: Enzym., 2013, 89, 28-34.
- 65 R. S. Wang, R. D. Chen, J. H. Li, X. Liu, K. B. Xie, D. W. Chen, Y. Z. Yin, X. Y. Tao, D. Xie, J. H. Zou, L. Yang and J. G. Dai, J. Biol. Chem., 2014, 289, 35815-35825.
- 66 Y. H. Jo, S. B. Kim, Q. Liu, S. G. Do, B. Y. Hwang and M. K. Lee, PLoS One, 2017, 12, e0172069.
- 67 X. X. Huang, H. F. Lai and Z. W. Li, Her. Med., 2013, 32, 664-666.
- 68 B. Li, M. Wang, Y. N. Tan, M. M. Tong and Y. J. Zhai, Zhongguo Zhongyao Zazhi, 2013, 38, 167-170.
- 69 J. S. Jeon, S. M. Kim, H. J. Lee, B. H. Um, H. K. Kim and C. Y. Kim, J. Liq. Chromatogr. Relat. Technol., 2012, 35, 1607-1615.
- 70 G. T. Jung, I. O. Ju, S. R. Choi, D. H. You and J. J. Noh, Korean Journal of Food Preservation, 2013, 20, 330-335.
- 71 L. Shi and Y. Fu, Acta Biochim. Biophys. Sin., 2011, 43, 418-424.
- 72 L. Shi, K. Chen, Q. Dong, J. Fang and K. Ding, Front. Chem. China, 2008, 3, 209-212.
- 73 L. Shi, Y. L. Fu and K. S. Chen, Fitoterapia, 2007, 78, 298-
- 74 L. Shi, Q. Dong and K. Ding, Food Chem., 2014, 152, 291-
- 75 Z. P. Zheng, H. Y. Tan, J. Chen and M. Wang, Fitoterapia, 2013, 84, 242-247.
- 76 V. K. Bajpai, A. Sharma and K. H. Baek, Food Control, 2013, 32, 582-590.
- 77 E. N. Novruzov and U. M. Agamirov, Chem. Nat. Compd., 2002, 38, 468-469.
- 78 E. J. Cho, T. Yokozawa, D. Y. Rhyu, S. C. Kim, N. Shibahara and J. C. Park, Phytomedicine, 2003, 10, 544-551.

- 79 H. S. Han, S. Y. Kim, D. J. Lim and W. K. Whang, Asian Journal of Beauty and Cosmetology, 2016, 14, 317-328.
- 80 T. J. Kim, H. J. Han, S. S. Hong, J. H. Hwang, B. Y. Hawang, H. S. Yoo, Y. R. Jin, J. J. Lee, J. Y. Yu, K. H. Lee, B. W. Kang and Y. P. Yun, Biol. Pharm. Bull., 2007, 30, 805-809.
- 81 H. J. Han, T. J. Kim, Y. R. Jin, S. S. Hong, J. H. Hwang, B. Y. Hwang, K. H. Lee, T. K. Park and Y. P. Yun, Planta Med., 2007, 73, 1163-1168.
- 82 J. E. Kim and K. W. Lee, Int. J. Mol. Sci., 2015, 16, 25096-
- 83 G. Yang, K. Lee, M. Lee, I. Ham and H. Y. Choi, BMC Complementary Altern. Med., 2012, 12, 250.
- 84 W. G. Seo, H. O. Pae, G. S. Oh, K. Y. Chai, Y. G. Yun, T. O. Kwon and H. T. Chung, Gen. Pharmacol. Vasc. Syst., 2000, 35, 21-28.
- 85 E. G. Lee, H. J. Yun, S. I. Lee and W. H. Yoo, Korean J. Intern. Med., 2010, 25, 93-100.
- 86 E. G. Lee, S. Lee, H. J. Chae, S. J. Park, Y. C. Lee and W. H. Yoo, Biol. Res., 2010, 43, 225-231.
- 87 H. L. T. Anh, D. T. Tuan, D. T. Trang, B. H. Tai, N. X. Nhiem, P. H. Yen, P. V. Kiem, C. V. Minh, T. M. Duc, H. K. Kang, Y. C. Kim and Y. H. Kim, J. Asian Nat. Prod. Res., 2016, 1-9.
- 88 Y. H. Jo, S. B. Kim, Q. Liu, B. Y. Hwang and M. K. Lee, Arch. Pharm., 2017, 350, e1600263.
- 89 S. K. Ku, M. S. Han, G. S. Jeong and J. S. Bae, Anim. Cells Syst., 2014, 18, 9-16.
- 90 S. J. Galli, M. Tsai and A. M. Piliponsky, Nature, 2008, 454, 445-454.
- 91 T. Lee, J. Kwon, D. Lee and W. Mar, J. Agric. Food Chem., 2015, 63, 5459-5467.
- 92 J. U. Shim and K. T. Lim, *Inflammation*, 2009, 32, 211–217.
- 93 J. Lee and K. T. Lim, Naunyn-Schmiedeberg's Arch. Pharmacol., 2010, 382, 51-61.
- 94 C. H. Park and K. T. Lim, Immunol. Invest., 2010, 39, 171-185.
- 95 P. S. Oh and K. T. Lim, J. Cell. Biochem., 2010, 109, 124-131.
- 96 P. S. Oh, K. Lim and K. T. Lim, Cell Biochem. Funct., 2010, 28, 352-359.
- 97 C. H. Jeong, G. N. Choi, J. H. Kim, J. H. Kwak, H. J. Heo, K. H. Shim, B. R. Cho, Y. Bae and J. S. Choi, Prev. Nutr. Food Sci., 2009, 14, 283-289.
- 98 J. Y. Kim, J. H. Chung, I. Hwang, Y. S. Kwan, J. K. Chai, K. H. Lee, T. H. Han and J. H. Moon, Korean J. Hortic. Sci. Technol., 2009, 27, 489-496.
- 99 Y. Lee, J. Oh, H. Lee, N. K. Lee, D. Y. Jeong and Y. S. Jeong, Biotechnol. Bioprocess Eng., 2015, 20, 861-870.
- 100 Y. Lee, J. Oh and Y. S. Jeong, Food Sci. Biotechnol., 2015, 24, 1817-1821.
- 101 N. S. Oh, J. Y. Lee, S. Oh, J. Y. Joung, S. G. Kim, Y. K. Shin, K. W. Lee, S. H. Kim and Y. Kim, J. Dairy Sci., 2016, 99, 1-12.
- 102 N. S. Oh, J. Y. Lee, J. Y. Joung, K. S. Kim, Y. K. Shin, K. W. Lee, S. H. Kim, S. Oh and Y. Kim, Appl. Microbiol. Biotechnol., 2016, 100, 5919-5932.
- 103 S. H. Nile and D. H. Kim, Nat. Prod. Commun., 2015, 10, 1839-1842.
- 104 G. R. Shin, S. Lee, S. Lee, S. Do, E. Shin and C. H. Lee, Ind. Crops Prod., 2015, 70, 322-331.

Review

- 105 J. H. Lee, B. W. Lee, J. H. Kim, W. D. Seo, K. C. Jang and K. H. Park, J. Appl. Biol. Chem., 2005, 48, 193-197.
- 106 W. G. Seo, H. O. Pae, G. S. Oh, K. Y. Chai, Y. G. Yun, H. T. Chung, K. K. Jang and T. O. Kwon, Am. J. Chin. Med., 2001, 29, 313-320.
- 107 S. B. Kwon, M. J. Kim, J. M. Yang, H. P. Lee, J. T. Hong, H. S. Jeong, E. S. Kim and D. Y. Yoon, PLoS One, 2016, 11,
- 108 Z. Zhang, H. J. Wu, N. H. Pi, T. Zhang, W. Y. Yuan, A. J. Hou and J. H. Liu, World Clin. Drugs, 2009, 30, 601-605.
- 109 Y. H. Rho, S. H. Yoon, E. K. Kim, J. Y. Kang, B. W. Lee, K. H. Park and Y. S. Bae, Nat. Prod. Res., 2007, 21, 616-624.
- 110 Y. H. Rho, B. W. Lee, K. H. Park and Y. S. Bae, Anti-Cancer Drugs, 2007, 18, 1023-1028.
- 111 S. H. Kim, S. H. Yoon, B. W. Lee, K. H. Park, Y. H. Kim and Y. S. Bae, Oncol. Res., 2005, 15, 327-332.
- 112 H. J. Lee, S. S. Jue, S. K. Kang, W. J. Bae, Y. C. Kim and E. C. Kim, Am. J. Chin. Med., 2015, 43, 1-14.
- 113 M. R. Shin, H. J. Lee, S. K. Kang, Q. S. Auh, Y. M. Lee, Y. C. Kim and E. C. Kim, BioMed Res. Int., 2014, 2014, 934691.
- 114 S. M. Jeon, D. S. Lee and G. S. Jeong, J. Ethnopharmacol., 2016, 194, 57-62.
- 115 Y. J. Choi, H. M. Kim and H. D. Kim, Arch. Pharmacal Res., 2009, 32, 59-63.
- 116 Y. H. Jo, B. Shin, Q. Liu, K. Y. Lee, D. C. Oh, B. Y. Hwang and M. K. Lee, J. Nat. Prod., 2014, 77, 2361-2366.
- 117 C. H. Jeong, G. N. Choi, J. H. Kim, J. H. Kwak, H. R. Jeong, D. O. Kim and H. J. Heo, Food Sci. Biotechnol., 2010, 19, 1113-1117.
- 118 X. H. Han, S. S. Hong, J. S. Hwang, S. H. Jeong, J. H. Jeong, J. H. Hwang, M. H. Lee, M. K. Lee, D. Lee, J. S. Ro and B. Y. Hwang, Arch. Pharmacal Res., 2005, 28, 1324-1327.
- 119 D. W. Kim, J. Kwon, S. J. Sim, D. Lee and W. Mar, J. Funct. Foods, 2017, 29, 104-114.
- 120 D. W. Kim, K. T. Lee, J. Kwon, H. J. Lee, D. Lee and W. Mar, Life Sci., 2015, 130, 25-30.
- 121 C. S. Yoon, D. C. Kim, T. H. Quang, J. Seo, D. G. Kang, H. S. Lee, H. Oh and Y. C. Kim, Molecules, 2016, 21, 1-12.
- 122 B. H. Kim, J. Kwon, D. Lee and W. Ma, Planta Med. Lett., 2015, 2, e15-e18.
- 123 J. Y. Lim, B. Y. Hwang, K. W. Hwang and S. Y. Park, Phytother. Res., 2012, 26, 1948-1956.
- 124 Y. H. Jo, S. B. Kim, Q. Liu, J. W. Lee, B. Y. Hwang and M. K. Lee, Bioorg. Med. Chem. Lett., 2015, 25, 3455-3457.
- 125 T. H. Quang, N. T. T. Ngan, C. S. Yoon, K. H. Cho, D. G. Kang, H. S. Lee, Y. C. Kim and H. Oh, Molecules, 2015, 20, 11173-11183.
- 126 D. H. Suh, E. S. Jung, H. M. Park, S. H. Kim, S. Lee, Y. H. Jo, M. K. Lee, G. Jung, S. G. Do and C. H. Lee, PLoS One, 2016, 11, e0149022.
- 127 Y. H. Jo, K. M. Choi, Q. Liu, S. B. Kim, H. J. Ji, M. Kim, S. K. Shin, S. G. Do, E. Shin, G. Jung, H. S. Yoo, B. Y. Hwang and M. K. Lee, *Nutrients*, 2015, 7, 10480-10490.
- 128 K. B. Lee, K. S. Song, E. H. Moon, J. Lee and Y. C. Yoo, J. Korean Soc. Appl. Biol. Chem., 2009, 52, 234-240.

- 129 P. S. Oh and K. T. Lim, Naunyn-Schmiedeberg's Arch. Pharmacol., 2009, 380, 115-124.
- 130 W. Palinski, M. E. Rosenfeld, S. Ylä-Herttuala, G. C. Gurtner, S. S. Socher, S. W. Butler, S. Parthasarathy, T. E. Carew, D. Steinberg and J. L. Witztum, Proc. Natl. Acad. Sci. U. S. A., 1989, 86, 1372-1376.
- 131 Y. S. Park, S. H. Kim, S. Y. Kim, G. M. Koh, J. H. Suh and J. S. Kang, *Pharmacol. Pharm.*, 2016, 7, 358–367.
- 132 H. Lee, H. Ha, J. K. Lee, C. Seo, N. Lee, D. Jung, S. Park and H. K. Shin, Phytother. Res., 2012, 26, 594-599.
- 133 S. T. Hu, Z. P. Zheng, X. C. Zhang, F. Chen and M. F. Wang, J. Funct. Foods, 2015, 13, 375-383.
- 134 O. K. Kim, W. J. Jun and J. M. Lee, *Nutrients*, 2016, 8, 60.
- 135 D. S. Lee and G. S. Jeong, Int. Immunopharmacol., 2014, 21,
- 136 D. G. Kang, T. Y. Hur, G. M. Lee, H. Oh, T. O. Kwon, E. J. Sohn and H. S. Lee, Life Sci., 2002, 70, 2599-2609.
- 137 Y. B. Ryu, M. J. Curtis-Long, J. W. Lee, H. W. Ryu, J. Y. Kim, W. S. Lee and K. H. Park, Bioorg. Med. Chem. Lett., 2009, 19, 4912-4915.
- 138 J. Sim, E. Choi, G. S. Jeong and S. Lee, Biopharm. Drug Dispos., 2015, 36, 325-336.
- 139 J. Sim, E. Choi, Y. M. Lee, G. S. Jeong and S. Lee, Food Chem. Toxicol., 2015, 81, 171-175.
- 140 N. H. Pi, J. Chen, J. M. Huang and A. J. Hou, J. Chromatogr. B: Anal. Technol. Biomed. Life Sci., 2010, 878, 1953-1958.
- 141 J. Xu, H. B. Chen and S. L. Li, Med. Res. Rev., 2016, 1-46.
- 142 C. T. Cao, C. L. Sun, W. B. Bai, J. X. Sun, G. Q. Li, S. Y. Ou and Y. Yang, Shipin Kexue, 2015, 36, 48-51.
- 143 C. Lei, C. C. Liu, E. H. Pi and A. J. Hou, Helv. Chim. Acta, 2014, 97, 1683-1688.
- 144 T. Nomura, Y. Hano and T. Fujimoto, Heterocycles, 1983, 20, 213-218.
- 145 J. Kwon, N. T. Hiep, D. W. Kim, S. Hong, Y. Guo, B. Y. Hwang, H. J. Lee, W. Mar and D. Lee, J. Nat. Prod., 2016, 79, 1938-1951.
- 146 Y. Hano, Y. Matsumoto, J. Y. Sun and T. Nomura, Planta Med., 1990, 56, 399-402.
- 147 Y. Hano, Y. Matsumoto, J. Y. Sun and T. Nomura, Planta Med., 1990, 56, 478-481.
- 148 Y. Hano, Y. Matsumoto, K. Shinohara, J. Y. Sun and T. Nomura, Planta Med., 1991, 57, 172-175.
- 149 Z. P. Zheng, J. Y. Liang and L. H. Hu, J. Integr. Plant Biol., 2006, 48, 996-1000.
- 150 T. Fujimoto, Y. Hano, T. Nomura and J. Uzawa, Planta Med., 1984, **50**, 161–163.
- 151 Y. Hano, Y. Matsumoto, K. Shinohara, J. Y. Sun and T. Nomura, Heterocycles, 1990, 31, 1339-1344.
- 152 W. C. Wu, Y. J. Zhai and Z. Y. Li, Zhongyaocai, 2010, 33, 913-
- 153 Y. Z. Yin, R. S. Wang, R. D. Chen, L. R. Qiao, L. Yang, C. M. Wang and J. G. Dai, Zhongguo Zhongyao Zazhi, 2012, 37, 3734-3737.
- 154 H. S. Young, J. H. Park, H. J. Park and J. S. Choi, Arch. Pharmacal Res., 1989, 12, 39-41.
- 155 G. M. Zhang, X. Y. Xu and J. F. Xi, Zhongchengyao, 2008, 30, 771-773.

156 Y. J. Lee, S. Kim, S. J. Lee, I. Ham and W. K. Whang, Arch.

- Pharmacal Res., 2009, 32, 195–200.
- 157 B. W. Lee, J. H. Lee, S. W. Gal, Y. H. Moon and K. H. Park, *Biosci., Biotechnol., Biochem.*, 2006, **70**, 427–432.
- 158 T. Fujimoto and T. Nomura, Planta Med., 1985, 51, 190-193.
- 159 W. G. Shan, L. L. Shi, Y. M. Ying, X. R. Hou and Z. J. Zhan, *J. Chem. Res.*, 2013, **37**, 285–286.
- 160 Y. Guan, Z. Yin, L. Guo, X. Huang, W. Ye and W. Shen, *Zhongguo Zhongyao Zazhi*, 2009, 34, 1108–1110.
- 161 A. K. Ibrahim, A. A. Mohamed and T. Mukul, *World J. Pharm. Res.*, 2014, 3, 981–997.
- 162 Y. Kang, J. U. Choi, E. A. Lee and H. R. Park, *Food Sci. Biotechnol.*, 2013, **22**, 1449–1452.

- 163 H. J. Lee, S. T. Cho, T. G. Lee, U. J. Kim, E. C. Ma and D. H. Lee, *Repub. Korean Kongkae Taeho Kongbo*, 2015, 5, 33.
- 164 C. P. Li, X. J. Chang, L. Fang, J. B. Yao, R. W. Wang, Z. J. Zhan, Y. M. Ying and W. G. Shan, *Chem. Nat. Compd.*, 2016, 52, 202–204.
- 165 A. P. Wang, M. C. Liu and S. J. Yang, *Chin. J. Exp. Tradit. Med. Formulae*, 2011, 17, 113–115.
- 166 C. H. Miu, Z. B. Gu and G. J. Yang, *Zhongchengyao*, 2002, **24**, 211–212.
- 167 Y. H. Zhang, W. W. Ren and S. W. Wan, Yiyao Gongye, 1980, 3, 15.
- 168 N. T. Hiep, J. Kwon, D. W. Kim, S. Hong, Y. Guo, B. Y. Hwang, N. Kim, W. Mar and D. Lee, *Tetrahedron*, 2017, 73, 2747–2759.