



The large-leaved Kudingcha (*Ilex latifolia* Thunb and *Ilex kudingcha* C.J. Tseng): a traditional Chinese tea with plentiful secondary metabolites and potential biological activities

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Received: 21 October 2012 / Accepted: 20 February 2013 / Published online: 26 March 2013
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Abstract In China, Kudingcha has been used for almost 2,000 years as a tea to quench thirst, remove phlegm, refresh the mind, and improve eyesight. The group of large-leaved Kudingcha is coveted for its potential effects on lipid metabolism, which are attributed to the presence of characteristic ingredients. This contribution reviews studies from the past few decades regarding the plant characteristics, ethnobotanical usages, chemical constituents, and related biological activities of the large-leaved Kudingcha (*Ilex latifolia* Thunb and *Ilex kudingcha* C.J. Tseng). Triterpenoids, phenolic acids, flavonoids, and essential oils are the main metabolites in the large-leaved Kudingcha, and these ingredients protect the vascular system, regulate lipid metabolism, and have antioxidant, hypoglycemic, and anti-tumor effects. Moreover, large-leaved Kudingcha shares several properties with the popular green tea and the Yerba maté from South America.

Keywords Large-leaved Kudingcha · *Ilex* · Plant characteristics · Ethnobotanical usages · Chemical constituents · Therapeutic properties · Yerba maté

Introduction

Kudingcha is a particularly bitter-tasting tea that has been widely used in China throughout history. It is known to disperse wind-heat, clear toxins from the blood, and refresh the mentalities. It has also been used to cure the common cold, rhinitis, itching eyes, conjunctival congestion, and headache; it is helpful for digestion and alleviating the adverse effects of alcohol [1, 2]. Today, nearly 20 plants from different families with similarities in appearance, flavor, and traditional usage in different areas of China are all named “Kudingcha” [3]. However, the plants most commonly found in the markets of China can be divided into 2 groups: one group, including species *Ilex latifolia* Thunb and *I. kudingcha* C.J. Tseng, was named the “large-leaved Kudingcha”; the other group, containing the species *Ligustrum robustum* (syn. *Ligustrum purpurascens*), was named the “small-leaved Kudingcha.” The large-leaved Kudingcha was certified to be the original Kudingcha species and has obvious antioxidant, anti-inflammatory, lipid metabolism, hepatoprotective, and anti-tumor activities [4–7], similar to the popular green tea (*Camellia sinensis*) and the Yerba maté tea (*Ilex paraguariensis*) from South America. Over the last several years, Kudingcha has been considered as a dietetic beverage and is gaining popularity with names like “beauty-slimming tea,” “longevity tea,” “green-golden tea,” and “clearing-heat tea.”

In the current review, we present and analyze the plant characteristics, ethnobotanical usages, phytochemistry, and pharmacological activities of the large-leaved Kudingcha, as well as its relationship with green tea and Yerba maté tea. These up-to-date research observations will be helpful in understanding the characteristics and superiorities of this special tea and would be applicable in developing new products and herbal medicines in the future.

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Historical and ethnopharmacological investigation of Kudingcha in China

In the book “Tong Jun Lu” (桐君录) (A.D. 25–225; E. Han Dynasty), Kudingcha was described as having a bitter flavor and reportedly kept people awake all night [8]. The original species in “Tong Jun Lu” were investigated and certified to be *I. latifolia*, *I. kudingcha*, and *I. cortia* [9]. At present, *I. cortia* is called “Gougucha” and is classified separately from Kudingcha due to its different botanical characters, chemical ingredients, and medicinal usages [11]. On the basis of our investigation of the literature, plant resources, and chemical and molecular analyses conducted since 2006, it appears that the large-leaved Kudingcha from the genus *Ilex* (*I. latifolia* and *I. kudingcha*) is the original Kudingcha species [2, 8, 11].

The medicinal properties of Kudingcha were reported in “Ben Cao Shi Yi” (本草拾遗) of the Tang Dynasty, including clearing the thirst and phlegm, resolving hydropsia, refreshing the mind, and improving the eyesight. In the encyclopedia “Ben Cao Gang Mu” (本草纲目) of the Ming Dynasty, Kudingcha was described as an effective herb that contained no toxins and had medicinal properties that could scatter wind-heat, refresh the mind and spirit, and promote fluid production to quench thirst [3]. The records in ancient books were all about the large-leaved Kudingcha from the genus *Ilex*. The current application of *I. latifolia* is limited to a few provinces of Eastern China. The supply and market share are limited compared to that of *I. kudingcha*.

The other important group (the small-leaved Kudingcha) from the genus *Ligustrum* was first reported in the book of “Guizhou Min Jian Fang Yao Ji” in 1958. Some investigators put forward that the small-leaved Kudingcha originated from the mountains of Dalou and the river valley of

Wujiang in Guizhou province. It has been used in the civilian Tujia ethnic group and Miao ethnic group for a long time, so was named as one of the four famous old tea species locally [2, 10]. No literal records have been found in ancient books to date. The small-leaved Kudingcha (*L. robustum*) was initially used because of its similarities in plant morphology, bitter flavor, and ethnobotanical use in folk medicine.

Plant characteristics and distribution of Kudingcha species

Two species of the large-leaved Kudingcha from the genus *Ilex* have very similar botanical appearances. Both come from trees that are evergreen, and the primary difference between the species is found at the base of the leaves [4]. The leaf characteristics of Kudingcha species are listed in Table 1. The small-leaved Kudingcha from the genus *Ligustrum* are shrubs or small trees, deciduous or evergreen. The leaves are much smaller and thinner than the large-leaved Kudingcha, and the flavor is not as bitter as, which makes it more suitable to drink routinely [8]. According to Table 1, the essential leaf characteristics of each species are useful to distinguish Kudingcha original plants. While these Kudingcha species are distributed across different locations over China, they have similar ethnopharmacological properties (Table 2).

Secondary metabolites of large-leaved Kudingcha

Triterpenoids, phenolic acids, flavonoids, and essential oils were isolated and identified from the large-leaved

Table 1 Leaf characteristics of the most commonly used Kudingcha [65, 66]

Leaf characteristics	<i>I. kudingcha</i>	<i>I. latifolia</i>	<i>L. robustum</i>
Blade	Oblong to oblong-elliptic	Oblong or ovate oblong	Lanceolate to subovate or elliptic
Petiole	2–2.2 cm, abaxially subrounded, rugose, adaxially sulcate, puberulent	Subterete, abaxially rugose, adaxially slightly impressed	2–8 mm, pubescent, groovy
Margin	Doubly serrate or densely serrate	Sparsely serrate	–
Base	Obtuse or cuneate	Rounded or broadly cuneate	Broadly cuneate or subrounded
Apex	Acute or short acuminate	Short or long acuminate	Long acuminate
Texture	Leathery	Thickly leathery	Papery
Mid vein	Raised and keeled abaxially, impressed and sparsely puberulent adaxially	Impressed adaxially	–
Lateral vein	Evident on both surfaces	Obscure abaxially, obvious adaxially	–
Vein-pair	5–7	–	–
Vein-angle	About 50°	–	–

Table 2 Distribution and medical uses of the most commonly used Kudingcha

Common name	Species	Distribution	Recorded uses [8]
Large-leaved Kudingcha	<i>I. kudingcha</i>	Guangxi, Guangdong, Hainan, Hunan	Clearing pathogenic summer-heat and detoxifying, treatment of the dehydration and abdominal pain
	<i>I. latifolia</i>	Zhejiang, Jiangxi, Jiangsu	Removing the excessive fire and noxious heat from the lung and spleen, removing the damp-heat pathogens in the large intestine to eliminate the dysentery, mental refreshing
Small-leaved Kudingcha	<i>L. robustum</i> (syn. <i>L. purpurascens</i>)	Guizhou, Yunnan, Sichuan	Mental refreshing, treatment of the pathogenic summer-heat, polydipsia and thirst, headache, conjunctival congestion

Kudingcha. Among different types of constituents, triterpenoids and polyphenols were considered to be the most important metabolites, with various bioactivities (summarized in Fig. 1).

Triterpenoids

The ursane-type triterpenoids with lactone at the position of C20 and C28 are called α -kudinlactone (48–57, 113), β -kudinlactone (58–69), and γ -kudinlactone (74–78) (Fig. 1), and are considered to be the most characteristic chemicals in the Kudingcha species. The chemical analysis showed that *I. kudingcha* had the highest total triterpenoid content. The β -kudinlactone was the main type of triterpenoid present in *I. latifolia*, while γ -kudinlactone and α -kudinlactone were not present in *I. latifolia*. At the same time, none of these characteristic kudiosides were detected in the supposititious species *I. pentagona* and *I. cornuta* of China, and the similar Yerba maté of South America [11]. In addition, oleanane-type (1–13) and lupane-type triterpenes (81–87) and their glycosides were also found in *I. latifolia* and *I. kudingcha*.

Phenolic acids

Phenolic acids with antioxidant activities have been found in recent years. The main types of phenolic acids found in large-leaved Kudingcha were polyphenols and related compounds [30, 32]. High-performance liquid chromatography (HPLC) analysis showed the presence of 6 of these derivatives, but no caffeine, in female and male leaves of *I. latifolia*. However, the levels of these derivatives varied from season to season. The current-year spring leaves showed the highest levels of caffeic acid derivatives (147–235 mg/g), while the current-year autumn leaves, old spring leaves, and old autumn leaves had lower amounts of the derivatives of 36, 24–44, and 31 mg/g, respectively. The levels of 4-*O*-caffeoyl quinic acid increased 3–6 times in current-year leaves from spring to autumn. The contents

of the caffeic acid derivatives in the female plant were similar to those in the old leaves of the male plant. These results suggest that the new spring leaves of *I. latifolia* would be a good source for antioxidants [33].

Flavonoids

Compounds 90–92 and 119–121 were the main flavones isolated from the large-leaved Kudingcha. They are also the primary constituents in the popular green tea.

Essential oils and other secondary metabolites

The essential oils have been studied by using gas chromatography coupled to mass spectrometry (GC/MS), which indicated the presence of alcohol, aldehyde, ketone, ether, fatty acids, and fatty acid ester [34, 35]. Other secondary metabolites such as phytosterols and polysaccharides were also isolated and identified [26, 41].

Biological activities

Regularly drinking Kudingcha as a herbal tea has a positive role in the prevention and treatment of cardiovascular and cerebrovascular diseases, diabetes, pharyngitis, and cancer, particularly for the relevant troublesome conditions of arteriosclerosis, hypertension, dizziness, insomnia, palpitations, and chest tightness caused by cardiovascular diseases [8]. The most important biological activity of the tea is lipid metabolism activity. Moreover, it has antioxidant and anti-tumor activities, and has effects on the hypoglycemic and vascular system, similar to green tea and Yerba maté [2].

Lipid metabolism activity

An acyl CoA cholesteryl acyl transferase (ACAT) catalyzes the intracellular esterification of cholesterol in various tissues, and inhibitors of ACAT may serve as new

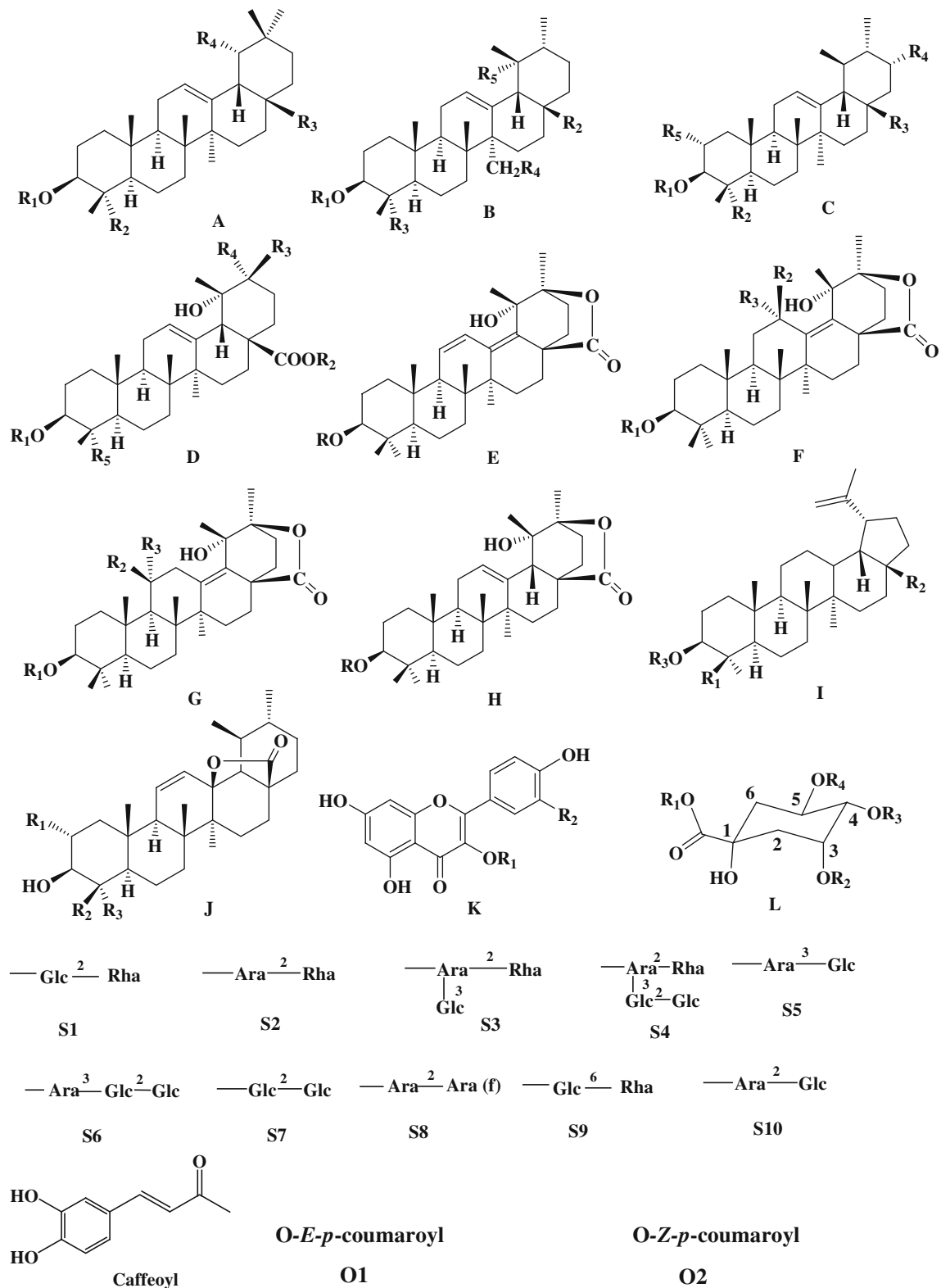


Fig. 1 The chemical structures of compounds isolated from the large-leaved Kudingcha

No.	Compound name	Skeleton	R1	R2	R3	R4	R5	Ref
1	β -amyrin	A	H	Me	Me	H	–	[22]
2	erythrodiol	A	H	Me	CH ₂ OH	H	–	[22]
3	oleanolic acid	A	H	Me	COOH	H	–	[22]
4	ilexosideXL VIII	A	GlcA	CH ₂ OH	COOGlc	H	–	[6]
5	ilekudinoside A (latifoloside O)	A	S3	Me	COOGlc	H	–	[6, 18]
6	mateglycoside D	A	S2	Me	COOGlc	H	–	[26]
7	latifoloside P	A	S2	Me	COOS1	H	–	[18]
8	latifoloside Q	A	S3	Me	COOS1	H	–	[18]
9	latifoloside B	A	S2	Me	COOGlc	OH	–	[15]
10	latifoloside C	A	S3	Me	COOGlc	OH	–	[15]
11	kudinoside N	A	S4	Me	COOGlc	OH	–	[19]
12	kudinoside O	A	S4	Me	COOS1	OH	–	[19]
13	latifoloside H	A	S3	Me	COOS1	OH	–	[17]
14	α -amyrin	B	H	Me	Me	H	H	[22]
15	ursolic acid 3-O-acetate	B	acetyl	COOH	Me	H	H	[22]
16	uvaol	B	H	CH ₂ OH	Me	H	H	[22]
17	uvaol 3-O-acetate	B	acetyl	CH ₂ OH	Me	H	H	[22]
18	ursolic acid	B	H	COOH	Me	H	H	[22]
19	3 β -palmitoyl- α -amyrin	B	CH ₃ (CH ₂) ₁₄ CO	Me	Me	H	H	[16]
20	23-hydroxyursolic acid	B	H	COOH	CH ₂ OH	H	H	[5]
21	27- <i>trans-p</i> -coumaroyloxyursolic acid	B	H	COOH	Me	O1	H	[5]
22	27- <i>cis-p</i> -coumaroyloxyursolic acid	B	H	COOH	CH ₂ OH	O2	H	[5]
23	ilekudinoside B	B	GlcA	COOGlc	Me	H	OH	[6]
24	ilekudinoside D	B	Ara	COOGlc	CH ₂ OH	H	OH	[6]
25	ilekudinoside E (latifoloside L)	B	S5	COOGlc	Me	H	OH	[6, 18]
26	kudinoside H	B	Ara	COOGlc	Me	H	OH	[14]
27	kudinoside G	B	S3	COOGlc	Me	H	OH	[14]
28	kudinoside L	B	S4	COOGlc	Me	H	OH	[19]
29	kudinoside P	B	S6	COOGlc	CH ₂ OH	H	OH	[19]
30	kudinoside M	B	S4	COOS1	Me	H	OH	[19]
31	latifoloside G	B	S3	COOS1	Me	H	OH	[17]
32	ilekudinoside W	B	S2	COOS1	Me	H	OH	[24]
33	latifoloside A	B	S2	COOGlc	Me	H	OH	[15]
34	latifoloside I (1)	C	S1	Me	CH ₂ OH	OGlc	H	[23]
35	latifoloside J (1)	C	S1	Me	COOH	OGlc	H	[23]
36	cynarasaponin C	C	Glc A	CH ₂ OH	COOGlc	H	H	[6]
37	ilekudinoside C	C	Ara	CH ₂ OH	COOGlc	H	OH	[6]
38	3- β -D-glucuronopyranosyl asiatic acid 28-O- β -D-glucopyranoside	C	Glc A	CH ₂ OH	COOGlc	H	OH	[19]

Fig. 1 continued

39	kudinoside I (1)	D	S3	S1	OH	Me	Me	[19]
40	kudinoside J (1)	D	S4	Glc	OH	Me	Me	[19]
41	kudinoside K	D	S4	S1	OH	Me	Me	[19]
42	latifoloside I (2)	D	S5	Glc	Me	H	Me	[18]
43	latifoloside J (2)	D	S2	S1	Me	H	Me	[18]
44	latifoloside K	D	S5	Glc	Me	H	CH ₂ OH	[18]
45	latifoloside C	D	S2	Glc	Me	H	Me	[15]
46	latifoloside D	D	S3	Glc	Me	H	Me	[15]
47	latifoloside F	D	S3	S1	Me	H	Me	[17]
48	α -kudinlactone	E	H	–	–	–	–	[14]
49	kudinoside D	E	S3	–	–	–	–	[14]
50	kudinoside E	E	S4	–	–	–	–	[14]
51	kudinoside J (2)	E	Ara	–	–	–	–	[14]
52	ilekudinoside K	E	S1	–	–	–	–	[20]
53	ilekudinoside N	E	S7	–	–	–	–	[20]
54	ilekudinoside O	E	S10	–	–	–	–	[20]
55	ilekudinoside P	E	S5	–	–	–	–	[20]
56	ilekudinchoside C	E	S8	–	–	–	–	[27]
57	ilekudinchoside D	E	S2	–	–	–	–	[27]
58	β -kudinlactone	F	H	OH	H	–	–	[14]
59	kudinoside B	F	S6	OH	H	–	–	[12]
60	kudinoside I (2)	F	Ara	OH	H	–	–	[14]
61	ilekudinoside J	F	S7	OH	H	–	–	[6]
62	ilekudinoside Q	F	S1	OH	H	–	–	[20]
63	kudinoside A (ilekudinchoside A)	F	S3	OH	H	–	–	[12, 27]
64	kudinoside C	F	S4	OH	H	–	–	[12]
65	ilekudinoside I	F	S10	OH	H	–	–	[6]
66	ilekudinoside L	F	S5	OH	H	–	–	[20]
67	ilekudinoside R	F	S2	OH	H	–	–	[20]
68	3-O- β -D-glucopyranosyl- β -kudinlactone	F	Glc	OH	H	–	–	[24]
69	ilekudinoside U	F	S3	EtO	H	–	–	[21]
70	ilekudinchoside B	F	S3	H	MeO	–	–	[27]
71	ilekudinchoside F	F	S3	H	EtO	–	–	[28]
72	ilekudinchoside G	F	S2	H	MeO	–	–	[28]
73	kudinoside LZ2	F	S3	O		–	–	[25]
74	kudinoside F	G	S3	OH	H	–	–	[14]
75	ilekudinoside H	G	S4	OH	H	–	–	[6]
76	ilekudinoside M	G	S2	OH	H	–	–	[20]
77	ilekudinoside S	G	S1	OH	H	–	–	[20]
78	ilekudinoside V	G	S3	O		–	–	[21]
79	ilekudinoside G	H	S4	–	–	–	–	[6]
80	ilekudinoside T	H	S3	–	–	–	–	[21]

Fig. 1 continued

81	lupeol	I	Me	Me	H	–	–	[22]
82	betulinic acid	I	Me	COOH	H	–	–	[22]
83	3 β -hydroxyl-lup-20(29)-24-methyl ester	I	COOMe	Me	H	–	–	[16]
84	3 β - palmitoyl-lup-20(29)-24-methyl ester	I	COOMe	Me	CH ₃ (CH ₂) ₁₄ CO	–	–	[16]
85	ilekudinol C	I	CH ₂ OH	CH ₂ OH	H	–	–	[5]
86	lup-20(29)-ene-3 β ,24-diol	I	CH ₂ OH	Me	H	–	–	[31]
87	betulin	I	Me	CH ₂ OH	H	–	–	[22]
88	13,28-epoxy- α -amyrin	J	H	Me	Me			[5]
89	ilekudinol A	J	OH	CH ₂		–	–	[5]
90	rutin	K	S9	OH	–	–	–	[61]
91	quercetin	K	OH	OH	–	–	–	[61]
92	kaempferol	K	OH	H	–	–	–	[61]
93	3-CQA (3-O-caffeoylquinic acid)	L	H	Caffeoyl	H	H	–	[30]
94	4-CQA	L	H	H	Caffeoyl	H	–	[30]
95	5-CQA	L	H	H	H	Caffeoyl	–	[30]
96	3,4-diCQA	L	H	Caffeoyl	Caffeoyl	H	–	[30]
97	3,5-diCQA	L	H	Caffeoyl	H	Caffeoyl	–	[30]
98	4,5-diCQA	L	H	H	Caffeoyl	Caffeoyl	–	[30]
99	4-CQA methyl ester	L	Me	H	Caffeoyl	H	–	[30]
100	3,4-diCQA methyl ester	L	Me	Caffeoyl	Caffeoyl	H	–	[30]
101	3,5-diCQA methyl ester	L	Me	Caffeoyl	H	Caffeoyl	–	[30]
102	4,5-diCQA methyl ester	L	Me	H	Caffeoyl	Caffeoyl	–	[30]
103	3,5-Di-O-caffeoyl epi-quinic acid butyl ester	L	Butyl	Caffeoyl	H	Caffeoyl	–	[30]
No	Compound name	ref	No	Compound name				Ref
104	ilekudinol B	5	115	ilekudinichoside E				[29]
105	ilelic acid A	51	116	CA methyl ester				[30]
106	ilelic acid B	51	117	caffeic acid				[30]
107	latifoloside N	18	118	cis-roseoside				[18]
108	latifoloside M	18	119	Epicatechin (EC)				[61]
109	ilelic acid C	51	120	Epigallocatechin gallate (EGCG)				[61]
110	ilelic acid D	51	121	Epicatechin gallate (ECG)				[61]
111	3-palmitoyl-11-carbonyl-urs-12-ene	16	122	mannitol				[31]
112	ilekudinoside F	6	123	vanillin				[26]
113	kudinchenin I	13	124	gallic acid				[26]
114	ulmoidol	5	125	ferulic acid				[26]

Fig. 1 continued

types of medicines to treat arteriosclerosis and obesity. Compounds **85**, **89**, **104**, **114**, and **20–22** isolated from *I. kudingcha* showed potent inhibitory activity in the ACAT assay. Compounds **104** (IC₅₀ 0.044 mM), **20** (IC₅₀ 0.064 mM), and **21** (IC₅₀ 0.073 mM) showed higher inhibitory activity than the other compounds (IC₅₀

0.154–0.468 mM) and those of lignans (IC₅₀ 25–207 mM) isolated from *Schisandra chinensis*, *Machilus thunbergii*, *Magnolia denudate*, *Magnolia ovata*, and the polyacetylenes (IC₅₀ 42–86 mM) from *Panax ginseng* [5].

Seventeen triterpenoids isolated from the aqueous extract of *I. kudingcha* were examined for inhibitory

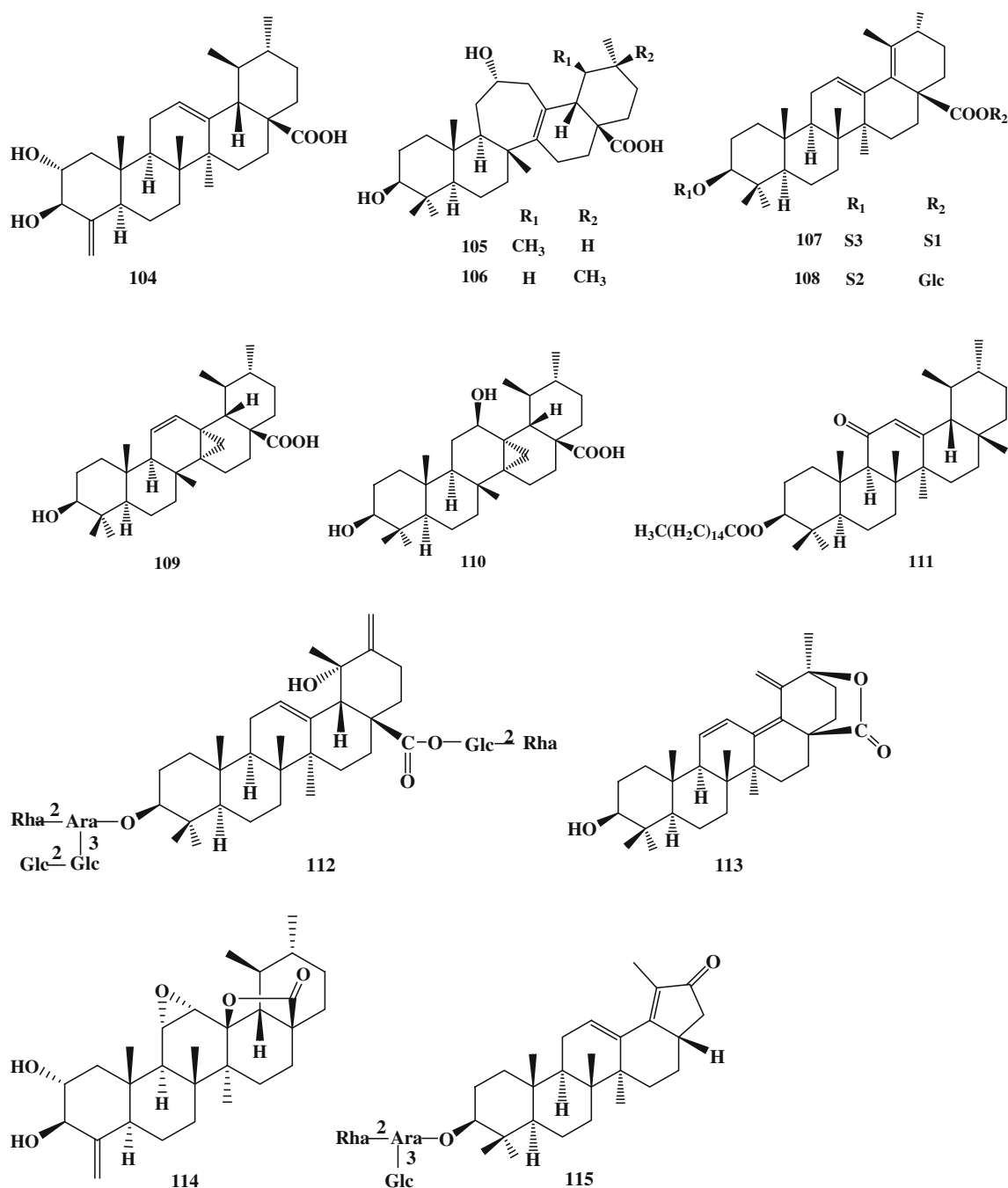


Fig. 1 continued

activity in the ACAT assay. Compounds **4** (the inhibitory activities were 64.3, 36.5, 15.7 % at 1.0, 0.2, 0.05 mg/mL, respectively) and **36** (the inhibitory activities were 63.9, 29.0, 31.7 % at 1.0, 0.2, 0.05 mg/mL, respectively) showed clear inhibitory activity [6].

A cell-based screening model using THP-1 macrophages was initially applied to aggregate LDL (aggLDL)-induced lipid deposition on macrophages to test the inhibitory effects of the 12 triterpenoids from *I. kudingcha*.

Compounds **63**, **64**, **49–53**, **55**, and **62** inhibited the formation of foam cells and reduced intracellular total cholesterol and triglyceride contents. The δ -lactone ring in the aglycone was indispensable to the biological activity. The OH group at the C-12 position, the number of monosaccharides in the sugar chain, and the presence of a terminal rhamnose residue in the sugar chain might improve this inhibitory effect. Moreover, compound **64** was considered as a potential candidate for the treatment of arteriosclerosis [53].

Medium and high doses of total saponins (150 and 300 mg kg⁻¹ day⁻¹, respectively) from *I. kudingcha* reduced the level of serum total cholesterol (TC) in ApoE-knockout mice (30–35 %), a reduction that was similar to the group treated with atorvastatin. It was likely that the saponins reduced the level of TC through the inhibition of ACAT activity. In addition, Kudingcha treatment led to greater inhibition of malondialdehyde (MDA) activity than atorvastatin [6, 36].

Protection of the vascular system

Various *Ilex* species were used in Chinese folk medicine to treat coronary heart diseases. The mode of action was considered to be mediated by their coronary vasodilative effects. The water extract of *I. latifolia* was shown to increase the contractility and decrease the frequency of contraction in an isolated rat heart perfusion system. The extract inhibited Na⁺/K⁺-ATPase activities in rat heart sarcolemma, rat brain microsome, and a purified enzyme from porcine cerebral cortex. It also inhibited Ca²⁺-dependent ATPase at a similar dose. Following exposure of the isolated rat heart to the extract at a dose that produces pronounced cardiac effects, the inhibition of Na⁺/K⁺-ATPase activity can be readily detected in the heart [7].

The water extract of *I. kudingcha* was able to increase coronary blood flow in isolated guinea pig heart and increase cerebral blood flow in anesthetized rabbits, prolong the survival time of mice under hypoxia, and protect rats from myocardial ischemia induced by pituitrin. The effects were beneficial in the prevention and treatment of coronary artery disease and angina pectoris [37].

Intravenous injection (0.05 g/kg) of the *I. kudingcha* extract remarkably lowered the blood pressure of normal anesthetized dogs. This hypotensive effect was also seen when the extracts (0.75 and 0.94 g/kg, respectively) were administered to 2-kidney, 1-clip hypertensive rats and spontaneously hypertensive rats by gastric gavage. The subcutaneous abdominal fatty tissue of normal and obese rats decreased significantly when the animals were given the extract (1.5 g/kg) by gastric gavage. The results suggested that *I. kudingcha* had potential as a resource for the treatment of hypertension and obesity [38].

Hypoglycemic effect

Caco-2 cells are derived from a human colon adenocarcinoma and are used widely as a model of intestinal absorption by epithelial cells and to study the absorption of glucose in vitro. Glucose absorption by Caco-2 cells was significantly inhibited by the aqueous extract of *I. kudingcha* under both Na⁺-dependent conditions and Na⁺-free

conditions, indicating an effect on SGLT1 and GLUT transporters. Analysis of the polyphenols in the extracts suggested that dicaffeoylquinic acids and flavanols may be particularly important in producing these effects. *I. kudingcha* was the most effective compared to the other plants tested, suggesting that it may merit evaluation in a clinical setting [39].

The water extract of *I. latifolia* showed marked inhibition of hyperglycemia in the epinephrine hyperglycemia rat model. The blood sugar levels of rats given either a low dose or a high dose of the extract (5 or 10 g/kg, respectively) were significantly reduced compared to the control group, indicating that *I. latifolia* has potential as a hypoglycemic drug [40].

Antioxidant activity

The antioxidant activities of *I. kudingcha* have been evaluated in vitro. The crude extract (CE), as well as the 4 fractions of chloroform (CfF), ethyl acetate (EaF), *n*-butanol (nBF), and water (WtF), were evaluated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical-scavenging assay, Trolox equivalent antioxidant capacity (TEAC), and ferric ion reducing antioxidant power (FRAP). The activities decreased in the order of EaF > nBF > CE > WtF > CfF, according to the DPPH and FRAP assays, with the exception of the rank order of CfF and WtF in the TEAC assay. The extracts were certified to contain a large number of caffeoylquinic acids (CQAs) (93–98), which contributed to the antioxidant activity. From a health point of view, Kudingcha is a beneficial herbal drink due to its antioxidant activity [32].

The ethyl acetate-soluble fraction of *I. kudingcha*, which contained an abundance of phenolic compounds, displayed remarkable free radical-scavenging activities against DPPH (IC₅₀ 16.3 μg/mL), ·OH (IC₅₀ 87.5 μg/mL for non-site-specific and 27.3 μg/mL for site-specific assays) and O₂⁻ (IC₅₀ 1.3 μg/mL). The fraction also showed a strong suppressive effect on rat liver mitochondrial peroxidation (IC₅₀ 7.1 μg/mL) and significantly protected against the oxidation of LDL mediated by either Cu²⁺ or AAPH free radicals (IC₅₀ were 14 and 4.8 μg/mL, respectively) [30].

The crude polysaccharide KPS II of *I. kudingcha* and 2 refined polysaccharides, KPS IIIa and KPS IIIb from KPS II, have concentration-dependent hydroxyl radical-scavenging activity. KPS IIIa and KPS IIIb were both composed of arabinose, xylose, mannose, galactose, and glucose, with molar ratios of 10.2:1.0:1.2:8.0:5.4 and 17.7:1.0:1.1:1.8:4.1, respectively. The scavenging capacity of the crude polysaccharide was higher than that of the refined polysaccharides [41].

The contents of total polyphenols and flavonoids of *I. latifolia* and *I. kudingcha* were detected by DPPH assay,

ABTS⁺ assay, OH-free radical-scavenging assay, reducing power assay, and FRAP assay, and were found to be correlated with their antioxidant activities. It was found that the water extract of *I. kudingcha* had both higher polyphenol content and better antioxidant performance than that of *I. latifolia* [42].

Antimicrobial activity

The studies of the anti-bacterial effect of *I. latifolia* showed an inhibitory effect on the growth of *Streptococcus A* [minimum inhibitory concentration (MIC) 1,215 mg/mL], *Pneumococcus* (MIC 25 mg/mL), *Streptococcus B* (MIC 25 mg/mL), *Bacillus diphtheria* (MIC 50 mg/mL), *Bacillus dysenteriae* (MIC 50 mg/mL), *Staphylococcus aureus* (MIC 100 mg/mL), *Pseudomonas aeruginosa* (MIC 100 mg/mL), *Escherichia coli* (MIC 100 mg/mL), and *Micrococcus catarrhalis* (MIC 200 mg/mL) by the agar dilution method in vitro. Intra-gastric administration can significantly improve the survival rate of mice infected by *E. coli*, *B. dysenteriae*, *Pneumobacillus*, and *Streptococcus B* [43].

The crude polysaccharides of *I. kudingcha* were tested against 7 bacterial and fungal strains commonly known to cause food spoilage, and the results showed that the polysaccharides had more significant activities against bacteria than fungi. The MIC against *S. aureus* was 5 mg/mL [44].

I. kudingcha was reported to have strong anti-bacterial activity against *S. aureus*, *Salmonella typhosa*, and β -hemolytic streptococci, as seen by the agar diffusion method. It could also enhance the action of hypoxia tolerance, hypothermia tolerance, and sports tolerance in the mouse, where it was shown to have anti-stress activities [45].

Antiviral activity

The anti-HSV-1 activities of different extracts of *I. kudingcha* were tested by cytopathogenic effect (CPE) observation and plaque reduction assay. The results showed that the aqueous extract had a more pronounced anti-HSV-1 effect (IC₅₀ 108.24 μ g/mL) and lower cytotoxicity (non-toxic concentration 500 μ g/mL) than the ethyl acetate and methanol extract. It is suggested that the extract acts by binding to the HSV-1 receptor and prevents the virus from entering the cells [46].

Studies were also conducted to measure the antiviral effects of *I. kudingcha* water extract against Coxsackie virus B3 (CVB3) cytotoxicity in HeLa cells by CPE and MTT methods. The results showed that this extract had a significant anti-CVB3 effect in vitro, yielding TC₅₀ values of 45700.3 μ g/mL, IC₅₀ values of 119.18 μ g/mL, and TI of 383.46 in HeLa cells [47].

Enhanced immunity

Aqueous extracts of *I. latifolia* were found to have beneficial effects on humoral and cellular immunity. The samples enhanced the phagocyte function of macrophages in the mouse abdominal cavity and increased the number of plaque-forming cells (PFCs), indicating that *I. latifolia* had potency as a new medicine to adjust and enhance the immune function of an organism [48].

To further study this effect, mice were immunocompromised by intragastric treatment with dexamethasone (DEX) for 7 days. The results showed that *I. latifolia* could improve the phagocytic index of macrophages, and high doses could distinctly enhance the number of PFCs and the percentage of phagocytic macrophages [49].

Anti-tumor activity

The anti-tumor activity of the ethanol extract and the volatile oils of the old leaves and fresh leaves of *I. latifolia* were tested by MTT assays. The results showed that the ethanol extract from the old leaves and the volatile oil from the fresh leaves had the most potent anti-tumor activity. For the ethanol extract of old leaves, the inhibition rate against human gastric cancer cells SGC-7901 was 62.40 %. For the volatile oil from the fresh leaves, the inhibition rates against human lung cancer cells NCI-H460 (IC₅₀ 42.86 mg/mL) and SGC-7901 were 93.33 and 32.44 %, respectively. The results provided a scientific basis for the use of the tea in the development of new anti-tumor medicines [50].

The growth inhibitory activities of compounds **105**, **106**, **109**, **110**, **21**, and **22** were evaluated in MCF-7 (estrogen receptor-positive) and MDA-MB-231 (estrogen receptor-negative) human breast cancer cells. Compounds **105** and **106** showed a growth inhibitory effect against MCF-7 cells, with IC₅₀ values of 29.51 \pm 3.44 and 38.49 \pm 3.16 μ M, respectively. Compound **21** (IC₅₀ 4.58 \pm 0.56 μ M) was the most potent among all the tested compounds, indicating that the *p*-(*E*)-coumaroyl moiety at the C-27 position may contribute to improving the growth inhibitory potential when compared with the triterpene with the *p*-(*Z*)-coumaroyl moiety (**22**, IC₅₀ 12.65 \pm 0.94 μ M). All the tested triterpenoids showed more potent growth inhibitory activity in MCF-7 cells than in MDA-MB-231 cells, implying that their growth inhibitory activities may be partly dependent on the status of the estrogen receptor [51].

The human nasopharyngeal carcinoma cell line NCE was divided into groups A (treated with 40 μ mol/L compound **18**), B (treated with DMSO 10 μ L), and C (without treatment), and the inhibition of cellular proliferation were detected by Western blotting at 12, 24, 48, 72, 96, and 120 h after treatment. The cellular proliferation in group A was remarkably inhibited at all time points, and the

inhibitory rate increased from 16.3 to 96.4 %. Under an optical microscope, the growth of NCE cells was inhibited, and the morphology changed after treatment. The Western blotting results showed that **18** could downregulate the expression of ERK and Cyclin D1 in a time-dependent manner. The data suggest that **18** could be used for treating nasopharyngeal carcinoma by downregulating the expression of ERK and Cyclin D1 in nasopharyngeal carcinoma cells [52]. In another study, an MTT assay was used to detect the effect of **18** on cellular proliferation, microscopy was used to observe cytotoxicity, and flow cytometry was used to detect apoptosis and cell cycle inhibition. The results showed that, within 24 h of treatment, 40 and 80 $\mu\text{mol/L}$ of **18** inhibited the proliferation of NEC-2 cells by 41.21 ± 0.25 and 94.11 ± 0.37 %, respectively. Both doses could block more than 70 % of cells at G0/G1. After 24 h of treatment with **18** (40 $\mu\text{mol/L}$), cell atrophy appeared, cell adhesion decreased, and some cells died from fragmentation [64].

Protective activity in neuronal cells

I. latifolia has been used in Chinese folk medicine to treat headaches and various inflammatory diseases. The protective activity of *I. latifolia* against glutamate-induced neurotoxicity was tested using cultured rat cortical neurons in order to understand the mechanism of its inhibitory effect on ischemic brain damage, and several potentially active compounds were identified. The exposure of cultured cortical neurons to 500 μM glutamate for 12 h triggered neuronal cell death. *I. latifolia* (10–100 $\mu\text{g/mL}$) inhibited glutamate-induced neuronal death, elevation of intracellular calcium ($[\text{Ca}^{2+}]_i$), generation of reactive oxygen species (ROS), increase of a pro-apoptotic protein, BAX, and decrease of an anti-apoptotic protein, Bcl-2. Hypoxia-induced neuronal cell death was also inhibited by *I. latifolia*. Compounds **98**, **99**, and **101** isolated from *I. latifolia* also inhibited the glutamate-induced increase in $[\text{Ca}^{2+}]_i$, generation of ROS, the change of apoptosis-related proteins, and neuronal and hypoxia-induced neuronal cell deaths. The results suggested that *I. latifolia* and its active compounds prevented glutamate-induced neuronal cell damage by inhibiting the increase of $[\text{Ca}^{2+}]_i$, generation of ROS, and, resultantly, the apoptotic pathway. In addition, the neuroprotective effects on ischemia-induced brain damage might be associated with the anti-excitatory and anti-oxidative actions, and could be attributable to these active compounds, CQAs [54].

Effect on pulmonary symptoms, including cough, asthma, and expectoration

The effects of *I. latifolia* on isolated guinea pig tracheal smooth muscle cells were evaluated by obtaining CaCl_2

and histamine accumulative dose–response curves in vitro. After incubation with the aqueous extract of *I. latifolia*, the dose–response curves of CaCl_2 and histamine were significantly shifted to the right and the maximal contractile force was reduced. The extract could inhibit the isolated tracheal strip contraction induced by acetylcholine and histamine (IC_{50} pf 0.16 and 0.21 mg/mL , respectively). It also had a significant dilating effect on tracheal smooth muscle, which indicated that *I. latifolia* had an important effect on pulmonary symptoms [55].

Toxicity

Kudingcha has been historically consumed as a functional tea, reflecting the philosophy of medicine–food homology in traditional Chinese medicine, with little or no acute toxicity. Acute and long-term toxicity of *I. latifolia* was studied in rats using aqueous extracts. The maximum tolerable dose was 168 g/kg , indicating that there is no acute toxicity. There were also no effects on body weight, hematopoiesis, and biochemical index in the blood of rats intragastrically treated with aqueous extracts at 4.5, 9, or 18 g/kg for 90 days [56].

Clinical usage

Studies have shown that drinking tea from both *I. kudingcha* and *I. latifolia* for 2 months is sufficient to reduce hypertension nearly as well as or better than common hypertension medications such as nifedipine [57, 58]. More importantly, no adverse reaction was observed. These studies suggested that *I. latifolia* and *I. kudingcha* have potential use in the treatment of hypertension.

The relationship between the large-leaved Kudingcha and related teas

Interestingly, the large-leaved Kudingcha from the genus *Ilex* has many similarities to Yerba maté tea (*I. paraguariensis*) from South America and the worldwide popular green tea (*C. sinensis*), a member of the Theaceae family [59]. These 3 teas have all been historically used and have shown antioxidant, lipid-lowering, anti-inflammatory, weight-reducing, anti-tumor, and anti-glycation properties [2, 5, 6]. These similarities could be ascribed to their similar phylogeny and chemical compositions.

In order to better understand the relationship among these teas, further comparison of the main chemical constituents of the large-leaved Kudingcha and the other 2 teas have been discussed. Most notably, the common chemical characters in regular tea are caffeine,

polyphenols, and catechins. Caffeine, which is related to weight reduction, is the highest in Yerba maté tea, medium in the green tea, and could not be found in the large-leaved Kudingcha [60, 61]. Polyphenols with conformed antioxidant activities are also the highest in Yerba maté tea, followed by green tea and large-leaved Kudingcha. The primary polyphenols in the large-leaved Kudingcha are 3,5-di-*O*-caffeoylquinic acid and related dicaffeoylquinic acids, whereas chlorogenic acid is the main polyphenol in Yerba maté tea. Catechins, which have anti-tumor properties, are the highest in green tea, followed by the large-leaved Kudingcha and Yerba maté tea [32, 62, 63]. Moreover, the saponins were thought to be the source of the bitter flavor and one of the important characteristics in the large-leaved Kudingcha and Yerba maté teas. The aroma components in *Ilex* and green tea also had several similarities.

The long history, similar chemical structure, and common pharmaceutical activities suggest a close genetic relationship among the large-leaved Kudingcha, Yerba maté tea, and green tea. Although the large-leaved Kudingcha is not as popular worldwide, we should pay more attention to its possible benefits and advantages, such as the lack of caffeine that is found in more ordinary teas.

Conclusions

A large number of phytochemical studies have led to the identification of multiple constituents of the large-leaved Kudingcha that confer properties such as lipid metabolism, vascular system protection, antioxidant, anti-asthma, anti-tussive, and anti-tumor activities. A critical assessment of the results presented in this review may provide scientific evidence for reasonable utilization of the original plants of the large-leaved Kudingcha and promote further investigation for the development of new herbal medicine and tea products. More pharmacological activities need to be undertaken and relevant mechanisms understood in order to enhance the utilization and quality of Kudingcha species in the future.

Acknowledgments This research was supported by the National Natural Science Foundation of China (no. 81274188).

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