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Lonicerae japonicae flos and Lonicerae flos: a systematic review of ethnopharmacology, phytochemistry and pharmacology

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Abstract Lonicerae japonicae flos (called Jinyinhua, JYH in Chinese), flowers or flower buds of *Lonicera japonica* Thunberg, is an extremely used traditional edible-medicinal herb. Pharmacological studies have already proved JYH ideal clinical therapeutic effects on inflammation and infectious diseases and prominent effects on multiple targets in vitro and in vivo, such as pro-inflammatory protein inducible nitric oxide synthase, toll-like receptor 4, interleukin-1 receptor. JYH and Lonicerae flos [called Shanyinhua, SYH in Chinese, flowers or flower buds of *Lonicera hypoglauca* Miquel, *Lonicera confusa* De Candolle or *Lonicera macrantha* (D.Don) Spreng] which belongs to the same family of JYH were once recorded as same herb in multiple versions of Chinese Pharmacopoeia (ChP). However, they were listed as two different herbs in 2005 Edition ChP, leading to endless controversy since they have close proximity on plant species, appearances and functions, together with traditional applications. In the past decades, there has no literature regarding to systematical comparison on the similarity concerning research achievements of the two herbs. This review comprehensively presents similarities and differences between JYH and SYH retrospectively, particularly proposing them the marked differences in botanies, phytochemistry and pharmacological activities which can be used as evidence of separate list of JYH and SYH. Furthermore, deficiencies on present studies have also been discussed so as to further research could use for reference.

Keywords *Lonicera japonica* Thunberg · Lonicerae flos · Phenolic acids · Macranthoside B · Toll-like receptor 4 · Interleukin-1 receptor

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Introduction

Lonicera japonica Thunberg (Caprifoliaceae), the medicine food homology herb (Hou and Jiang 2013) which has long been applied in treating inflammation and infectious diseases, is pervasively cultivated in eastern Asia, such as China, Japan and Korea (http://www.efloras.org/) and was initially introduced to

America as a horticultural plant with wind breaker and sand-fixation properties (He et al. 2017). However, it is now believed as a bio-invasion in North America, South America and Oceania (Lloyd et al. 2003). According to '*Ben Cao Gang Mu*' (AD 1552–1578), the herbalism masterpiece which was known as the ancient Chinese encyclopedia, JYH was described as a commonly used herb to treat fever, phyma and sore. Modern pharmacological study has confirmed the antiviral, antibacterial and anti-inflammatory activities of JYH, supporting the traditional applications (Kang et al. 2004; Kao et al. 2015; Shi et al. 2016). Likewise, pharmacological study showed antioxidative, anti-tumour, liver protective and hypoglycemic activities of JYH (Jiang et al. 2014; Kong et al. 2017; Zhao et al. 2018; Park et al. 2012a). So far, more than 300 compounds have been isolated and identified from JYH, including phenolic acids, flavonoids, saponins, iridoids, etc. (Yang et al. 2016; Ni 2017; Lin et al. 2008).

JYH is one of the 70 most valuable herbs declared by the State Council of China. There are 312 Chinese patent medicines (CPMs) and 163 domestic health food containing JYH according to the data of National Scientific Data Sharing Platform for Population and Health (http://www.ncmi.cn/) and China Food and Drug Administration (CFDA, www.sfda.gov.cn/). The standard of JYH was first recorded in Chinese Pharmacopoeia (ChP) in 1963, limiting JYH medicinal part to dried flower buds of *Lonicera japonica* Thunberg. In 1977 Edition ChP, JYH had four plant origins, including *L. japonica*, *Lonicera hypoglauca* Miquel, *Lonicera confusa* DeCandolle and *Lonicera dasystyla* Rehder. Meanwhile, the medicinal parts were dried flower buds or initial flowers. This standard did not change in the subsequent 1985, 1990, 1995, and 2000 Edition ChP. In 2005 Edition ChP, JYH and Lonicerae flos (called Shanyinhua, SYH in Chinese) were listed as two herbs. The plant origin of JYH was changed to be consistent with that of 1963 Edition ChP, being *L. japonica*, while SYH was a multi-origins herb and plant origins were *L. hypoglauca*, *L. confusa* and *Lonicera macranthoides* Handel-Mazzetti. In 2010 Edition ChP, *Lonicera fulvotomentosa* Hsu et Cheng was listed as a new plant origin of SYH. Since then, there have been four plant origins of SYH.

Since JYH and SYH were listed as two herbs, controversies on their quality standards and interchangeability are ceaselessly due to their close proximity on plant species and appearances, together with traditional applications and great homogeneity regarding their medicinal uses. Meanwhile, owing to higher price of JYH, JYH is often adulterated with SYH motivated by economic interests. Furthermore, pharmaceutical companies need to provide scientific evidence to the Pharmacopoeia Committee if they want to change crude materials in CPMs from JYH to SYH (http://samr.cfda.gov.cn/WS01/CL0844/10570.html). Last but not least, there is a synonymy problem of SYH plant origins that was not mentioned in ChP. According to ThePlantList and eFloras, *L. macranthoides* and *L. fulvotomentosa* are synonymies of *Lonicera macrantha* (D.Don) Spreng, and *L. dasystyla* is actually a synonymy of *L. confusa* (http://flora.huh.harvard.edu/china/mss/volume19/Flora_of_China_Volume_19_Caprifoliaceae.pdf, http://www.theplantlist.org/tpl1.1/record/kew-2339927). Hence, a complete review on similarities and differences of JYH and SYH is timely. In this review, we introduce botanies and ethnopharmacology of JYH and SYH, and discuss their similarities and differences with respect of phytochemistry, pharmacological activities and toxicology by systematically reviewing studies performed on JYH and SYH in recent decades. A critical evaluation of pharmacological studies in terms of their relation to ethnopharmacology is also provided. We generalize factors that affect their qualities and present quality control methods. Meanwhile, bioavailability of major compounds and clinical uses of JYH productions have also been mentioned. Above all, we provide an accurate cognition of JYH and SYH, and propose deficiencies on present studies so as to further research can use for reference.

Botany and ethnopharmacology

Botany

The order Dipsacales comprises a monophyletic taxon with two major lineages, namely Caprifoliaceae (including Valerianaceae, Dipsacaceae, Diervilleae, Caprifolieae, Linnaeeae and Morinaceae) and Adoxaceae (Fan et al. 2018; Group et al. 2016). In addition, Caprifolieae clade contains *Leycesteria* (6 species), *Lonicera* (about 200 species), *Symphoricarpos* (about

15 species) and *Triosteum* (6 species) (Theis et al. 2008), among which the genera *Lonicera* and *Triosteum* have a very close relationship (Fan et al. 2018). There are two subgenera in *Lonicera*, namely *Chamaecerasus* (or *Lonicera*) and *Periclymenum* (or *Caprifolium*) with approximately 150 and 20 species, respectively (Rehder 1903).

JYH

According to eFloras (http://www.efloras.org/florataxon.aspx?flora_id=2&taxon_id=118877) and 2015 Edition ChP, *L. japonica* is semi-evergreen climber. Branches, petioles, and peduncles with dense and yellow–brown spreading stiff hairs intersperse with long glandular hairs. Petioles are 3–8 mm. Leaves blades are ovate or oblong to lanceolate and they abaxially are sparsely to densely hairy, adaxially hairy along veins. Flowers are fragrant, paired and axillary toward apices of branchlets. Peduncles are 2–40 mm. Bracts are leaflike, ovate to elliptic. Bracteoles are pubescent, apex round or truncate and ciliate. Calyx lobes are triangular and densely hairy abaxially. Bilabiate corollas are hairy spreading with interspersing long glandular hairs outside. JYH is rod-shaped, slightly curved and 2–3 cm long, upper diameter about 3 mm, lower diameter about 1.5 mm. JYH is yellow–white or green–white, densely pubescent. The flowering phase ranges from May to September, and could be divided into six stages, the juvenile bud stage, the third green stage, the second white stage, the complete white stage, the silver flowering stage and the gold flowering stage (S1-S6) (Wang et al. 2009c).

L. japonica usually grows in scrub, sparse forests, mountain slopes, stony places or roadsides at an altitude of 800–1500 m (http://www.efloras.org/florataxon.aspx?flora_id=2&taxon_id=118877). As an ornamental and economic plant, *L. japonica* is cultivated or naturally distributed in most provinces of China (Li et al. 2013; Wang et al. 2008). Henan and Shandong provinces are considered as its main genuine producing areas (Shang et al. 2011). Miyinhua (production name, from Henan province), the geo-authentic crude drug (GCD) is famous for its long cultivation history and remarkable efficacy. The amount of Jiyinhua (production name, GCD from Shandong province) accounts for 35% of the total amount of JYH in China (http://www.jyhzj.com/).

SYH

SYH is semi-evergreen climbers with fragrant and paired flowers. Botanical traits of inflorescences and bracts are strategic points to differentiate four origins of SYH (Table 1; Fig. 1). Its flowering phase is April to September.

Four origins of SYH are widely cultivated in southern provinces of China. Wild plants grow in forests of mountain valleys or slopes, scrub, riversides, streamside or roadsides at an altitude of 200–2900 m (http://www.efloras.org/). Among them, *L. macranthoides* is the most cultivated one and dominates the current market, even popular than JYH. *L. confusa* is cultivated rarely and barely used (Chen et al. 2015a).

On the basis of '*Ben Cao Gang Mu*' and '*Zhi Wu Ming Shi Tu Kao*' (AD 1841–1846), the plant origin of JYH was typical climber with paired and opposite flowers axillary toward apices of branchlets. Ovate leaves were adaxially hairy along veins. Only *L. japonica* complies with the ancient records of JYH, whereas four origins of SYH are markedly different.

In sharp contrast with explicitly mono origin of JYH, a gap exists in the synonyms confusion of SYH origins. *L. dasystyla* is a synonym of *L. confusa* (www.theplantlist.org/, http://www.efloras.org/). However, they are regarded as different herbs by not a few researchers nowadays (Ou et al. 2011; Lim 2014). This is possibly due to they were once listed as two herbs in ChP for quite a long time. Moreover, *L. macranthoides* and *L. fulvotomentosa* were listed as two different plants in 2010 and 2015 Edition ChP, while they were synonyms of *L. macrantha* according to The Plant List and eFloras (www.theplantlist.org/, http://www.efloras.org/). As far as current research is concerned, it is difficult to point out their similarities or differences. Thereby studies on genetic diversity and relationships should be conducted. An evaluation of pharmacological studies of them should also be highlighted.

Ethnopharmacology

Lonicerae japonica was first recorded in '*Shen Nong Ben Cao Jing*' in the Eastern Han Dynasty (AD 25–220) and stems were used medicinally at that time. In '*Ben Cao Shi Yi*' (the Tang Dynasty, AD 618–709), stems of *L. japonica* were used to treat bloody dysentery. In '*Su Shen Liang Fang*' (the Northern

Table 1 Botanical traits comparison of four origins of SYH (http://www.efloras.org/)

Botanical traits	*L. macranthoides (L. macrantha)*	*L. hypoglauca*	*L. confusa* (*L. dasystyla*)	*L. fulvotomentosa (L. macrantha)*
Color and glandular hairs	Yellow or yellow–green	Yellow–white to yellow–brown, glabrous or sparse	Gray–brown to yellow–brown, densely gray–white hairs	Pale yellow–brown or yellow–brown, densely yellow hairs
Flower branches	Conical-like inflorescences of paired flowers, densely in axils	Short raceme inflorescences, single-paired flowers in axils	Short raceme inflorescences, single-paired flowers in axils	Short raceme inflorescences, single-paired flowers in axils
Bracts	Lanceolate	Lanceolate	Lanceolate	Filate
Texture of leaves	Leathery	Papery	Papery	Papery
Leaves	Orange–yellow glandular hairs	Abaxially large sessile orange glandular hairs	Dense glandular hairs	Densely filemot glandular hairs
Medicinal part	Rod-shaped, slightly curved, 3–4.5 cm long, upper diameter about 2 mm, lower 1 mm	2.5–4.5 cm long, diameter 0.5–2 mm	1.6–3.5 cm long, diameter 0.5–2 mm	1–3.4 cm long, diameter 1.5–2 mm

Fig. 1 **a** *L. japonica*, **b** *L. macranthoides,* **c** *L. hypoglauca*, **d** *L. confusa*, **e** *L. fulvotomentosa* (www.sfda.gov.cn/)

Song Dynasty, AD 960–1127), stems were considered as anti-inflammatory agents. Based on '*Dian Nan Ben Cao*' (the Ming Dynasty, AD 1368–1644), the main function of stems was to cure ulcer and sore. In '*Ben Cao Gang Mu*' (the Ming Dynasty, written later than '*Dian Nan Ben Cao*'), flowers were used as medicine for the first time. Besides, flowers, stems and leaves of *L. japonica* had the same efficacy when it comes to treatment of swelling and scabies (Table 2).

Nowadays, flowers as well as other parts, particularly stems and leaves, of the five *Lonicera* species are applied to clean heat and toxic, expel wind and cool blood in traditional Chinese medicine, while JYH and SYH actually concern dried flower buds or initial flowers only. According to 2015 Edition ChP, stems of *L. japonica* are used medicinally, called Lonicera Japonica Caulis. Yet leaves, non-medicinal part of *L. japonica*, have not been fully utilized. Modern studies have confirmed that flowers, stems and leaves of *L. japonica* have similar chemical compounds with a variety of pharmacological activities. Flavonoids in *L. japonica* were degressively abundant in leaves, flowers and stems, and leaves showed the highest antioxidative intensity than those of flowers or stems (Seo et al. 2012). Tian found that phenolic acids in flowers and leaves were similar and both were higher than that in stems (Tian et al. 2019), and these results could also be found in SYH (Chen et al. 2015b; Yuan et al. 2014). Meanwhile, powder of SYH leaves has already been used as dietary supplementation in animal diets (Long et al. 2016). In China, JYH has been used as tea for a long time. The sales of Wanglaoji (trade name), a tea beverage containing JYH, exceeded that of Coca-Cola in 2018. The supply of JYH is not adequate to the demand (http://www.sohu.com), while leaves of *L. japonica* are wasted greatly despite having a long history as tea (Wang et al. 2008). Leaves of *L. japonica* have been considered as medicinal part in

Table 2 Traditional uses of *L. japonica*

No.	Prescription name	Main herbs/used part	Traditional use	Administration and application area	Reference
1	Yinju Baihu Decoction	JYH, dried capitulum of *Chrysanthemum indicum* Linnaeus, Gypsum	Clearing heat and toxic, and expelling superficial evils	Oral	'Qianjin Miaofang'
2	Yinqiao Powder	JYH, dry fruits of *F. suspensa*	Curing headache, fever and cough	Oral	'Wenbing Tiaobian'
3	Yinhua Decoction	JYH, dried roots of *Astragalus membranaceus* (Fisch.) Bunge or *A. membranaceus* (Fisch.) Bunge var. *mongholicus* (Bunge) Hsiao	Curing phyma and relieving pain	Oral	'Zhulin Nvke Zhengzhi'
4	Jinyin Powder	JYH	Curing carbuncle and sore	External use	'Yangshi Jiachang Fang'
5	Jinyin Jiedu Decoction	JYH, dried bulbs of *Fritillaria thunbergii* Miquel	Curing acne and scab	Poultice External use	'Youke Zhiyan'
6	Simiao Yongan Decoction	Dried roots of *Scrophularia ningpoensis* Hemsley, JYH	Promoting blood circulation and relieving pain	Oral	'Yanfang Xinbian'
7	Liuwu Jiedu Decoction	Dried roots of *Smilax glabra* Roxburgh, JYH, dried roots of *Ligusticum chuanxiong* hortulanorum	Curing sore, distending pain	Oral	'Meili Xinshu'
8	Wushen Decoction	Dried sclerotia of *Poria cocos* Wolf, dried ripe fruits of *Plantago asiatica* Linnaeus or *Plantago depressa* Willdenow, JYH	Curing carbuncle	Oral	'Bianzheng Lu'
9	Xiaohua Decoction	JYH, Begonia fimbristipula, dried roots of *Trichosanthes kirilowii* Maximowicz or *Trichosanthes rosthornii* Harms	Clearing heat and toxic, promoting blood circulation and eliminating phlegm	Oral	'Waike Milu'

Japan and Korea according to the Japanese Pharmacopoeia and the Korean Pharmacopoeia. Therefore, in China, leaves of *L. japonica* and SYH origins should be valued in further studies.

JYH is typically matched with *Forsythia suspensa* (Thunberg) Vahl (Oleaceae) to clear heat and toxic, thereby curing seasonal febrile disease and sore. Another combination of JYH and *Scutellaria baicalensis* Georgi (Lamiaceae) is commonly used for the treatment of cough caused by lung fire. Shuang–Huang–Lian (SHL), a combination of JYH, *F. suspensa* and *S. baicalensis*, is the most typical formula to explain the traditional use of JYH. As a classic formula, SHL has been used for the treatment of cough, sore throat and fever, acting by dispelling wind, clearing heat and detoxification (Han et al. 2018; Tang et al. 2018; Tian et al. 2018). Till now, SHL has also been used extensively, and its preparations involve granules, oral liquid, injection, etc.

According to 2015 Edition ChP, JYH is developed into 87 CPMs in dosage form of pill, granules and liquid pharmaceutical preparations for oral consumption and multiple external preparations such as suppositories, eye drops, electuary, injection, etc. Additionally, 14 CPMs containing SYH are recorded, which are in dosage form of 13 oral preparations and1 external spraying agent (Table 3).

In brief, JYH recorded in ancient books should be *L. japonica* rather than any four origins of SYH according to the classical Chinese medical treatises. Genetic diversity and pharmacological studies of *L. macranthoides* and *L. fulvotomentosa* should be high-lighted. *L. japonica* has been successfully used medicinally in China for over 2000 years. Nowadays stems and flowers of *L. japonica* are traditionally and ethnobotanically used to cure sore, carbuncle, scab, erysipelas, distending pain, etc., generally, while leaves have similar efficacy with flowers based on the reported literature but are not utilized well, which need to be further investigated for solving the ongoing short supply of JYH.

Table 3 Preparations of JYH and SYH listed in 2015 Edition ChP

Name	Type	Main herbs	Function
JYH			
Yinhuang	Oral liquid	JYH, Scutellariae Radix	Curing acute and chronic tonsillitis and upper respiratory tract infection
Jinyinhua	Distilled liquid	JYH	Clearing heat and toxic. Curing pimples and sore throat
Xiaoer Yanbian	Granule	JYH, Belamcandae Rhizoma	Curing sore throat, cough and phlegm
Jingqi Jiangtang	Tablet	Coptidis Rhizoma, Astragali Radix, JYH	Curing light and moderate Type 2 diabetes
Niuhuang Jingnao	Tablet	Bovis Calculus Artifactus, JYH	Curing mania and dizziness caused by excessive heat
Lianhua Qingwen	Granule	Forsythiae Fructus, JYH	Curing influenza
Shuanghu Qinggan	Granule	JYH, Polygoni Cuspidati Rhizoma et Radix	Curing nausea, anorexia and chronic hepatitis B
Shuanghuanglian	Suppository	JYH, Forsythiae Fructus, Scutellariae Radix	Curing cold caused by exogenous wind and heat
SYH			
Fengreqing	Oral liquid	SYH, Bear bile powder	Curing colds, headache, cough, thirst
Fufang Zhenzhu Anchuang	Tablet	SYH, Taraxaci herba	Curing acne
Yinqiao Shangfeng	Capsule	SYH, Forsythiae Fructus	Curing exogenous wind-heat, febrile disease at the beginning
Yinpujiedu	Tablet	SYH, Taraxaciherba	Curing wind-heat acute pharyngitis and damp-heat pyelonephritis
Qinggan Lidan	Oral liquid	Artemisiae Scopariae Herba, SYH	Curing dumbness and hypochondriac pain induced by damp-heat congestion of liver and gallbladder

Table 4 Compounds presenting in JYH and/or SYH

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
Phenolic acids									
Chlorogenic acids derivatives common for JYH and SYH									
1	Chlorogenic acid	Whole plant	Distilled water	Peng et al. (2000)	Flower buds	n-Butyl alcohol	1, 2, 3, 4	Yang et al. (2016)	1794427
2	Neochlorogenic acid	Flower buds	95% ethanol	Jin-qian et al. (2016)	Flowers/flower buds	Distilled water	1	Yang et al. (2016)	5280633
3	Isochlorogenic acid A	Unknown	Unknown	Chang and Hsu (1992)	Flowers/flower buds	Distilled water	1, 2, 3, 4	Yao et al. (1986), Dan et al. (2008)	6474310
4	Isochlorogenic acid B	Unknown	Unknown	Chang and Hsu (1992)	Flowers/flower buds	Distilled water	1, 2, 3, 4	Yao et al. (1986), Dan et al. (2008)	5281780
5	Isochlorogenic acid C	Unknown	Unknown	Chang and Hsu (1992)	Flowers/flower buds	Distilled water	1	Yao et al. (1986)	6474309
6	Cryptochlorogenic acid	Flower buds	95% ethanol	Jin-qian et al. (2016)	Flowers/Flower buds	Distilled water	1	Yao et al. (1986)	9798)666
7	Cynarin	Unknown	Unknown	Iwahashi et al. (1986)	Flower buds	Distilled water	1	Zhang et al. (2016)	5281769
8	Methyl chlorogenate	Flower buds	Ethanol	Lee et al. (2010a)	Flower buds	n-Butyl alcohol	4	Chai et al. (2004b)	6476139
Chlorogenic acids derivatives only for JYH									
9	1,5-*O*-Dicaffeoylquinic acid	Leaves	Distilled water	Chan-juan and Si-ping (2010)					122685
10	1,4-*O*-Dicaffeoylquinic acid	Leaves	Distilled water	Chan-juan and Si-ping (2010)					12358846
11	5-p-Coumarylquinic acid	Leaves/ Flowers/ Stems	70% methanol	Seo et al. (2012)					6441280
12	Feruloylcaffeoylquinic acid	Leaves/ Flowers/ Stems	70% methanol	Seo et al. (2012)					
13	Chlorogenic acid butyl ester	Unknown	Unknown	Wang (2010)					
14	Methyl 3,5-di-*O*-caffeoylquinic acid	Whole plant	Unknown	Chang et al. (1995)					

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
15	Methyl 3,4-di-*O*-caffeoylquinic acid	Whole plant	Unknown	Chang et al. (1995)					5319160
16	3-*O*-Caffeoylquinic acid ethyl ester	Flower buds	Ethanol	Lee et al. (2010a)					
17	5-*O*-Caffeoylquinic acid butyl ester	Flower buds	Ethanol	Lee et al. (2010a)					
18	5-*O*-Caffeoylquinic acid methyl ester	Flower buds	Ethanol	Lee et al. (2010a)					54585255
19	3,5-*O*-Dicaffeoylquinic acid methyl ester	Flower buds	Unknown	Peng et al. (2000)					
20	3,5-*O*-Dicaffeoylquinic acid butyl ester	Flower buds	Unknown	Peng et al. (2000)					
21	3,5-*O*-Dicaffeoylquinic acid ethyl ester	Flower buds	Boiling water	Zheng et al. (2012)					
22	3,4-*O*-Dicaffeoylquinic acid methyl ester	Flower buds	Boiling water	Zheng et al. (2012)					
23	3,4-*O*-Dicaffeoylquinic acid ethyl ester	Flower buds	Boiling water	Zheng et al. (2012)					
24	4,5-*O*-Dicaffeoylquinic acid methyl ester	Flower buds	Boiling water	Zheng et al. (2012)					
25	(−)-4-*O*-(4-*O*-β-D-glucopyranosylcaffeoyl) quinic acid	Flower buds	Unknown	Yu et al. (2015a)					
26	(−)-3-*O*-(4-*O*-β-D-glucopyranosylcaffeoyl) quinic acid	Flower buds	Unknown	Yu et al. (2015a)					
27	(−)-5-*O*-(4-*O*-β-D-glucopyranosylcaffeoyl) quinic acid	Flower buds	Unknown	Yu et al. (2015a)					
Chlorogenic acids derivatives only for SYH									
28	5-*O*-Caffeoyl quinic acid butyl ester				Flower buds	n-butyl alcohol	4	Chai et al. (2004b)	6481825
29	3,4-Dicaffeoylquinic acid methyl ester				Flower buds	Ethyl acetate	2	Tang et al. (2007)	
30	4,5-Dicaffeoylquinic acid methyl ester				Flower buds	Ethyl acetate	2	Tang et al. (2007)	
31	Ethyl-3-*O*-caffeoylquinate				Flower buds	n-butanol	1	Hu et al. (2016)	

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
32	Butyl 5-caffeoyl quinine				Unknown	Unknown	Unknown	Chai et al. (2004b)	
33	3,4,5-tri-*O*-Caffeoylquinic acid				Flower buds	n-butanol	1	Hu et al. (2016)	6440783
34	Ethyl-4,5-di-*O*-caffeoylquinate				Flower buds	Distilled water	1	Zhang et al. (2016)	
35	Caffeoylshikimic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	25243950
36	2-Caffeoylshikimic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	
37	3-Caffeoylshikimic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	10131826
38	4-Caffeoylshikimic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	49821869
39	5-Caffeoylshikimic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	5281762
40	6-Caffeoylshikimic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	
41	3,4,5-tri-*O*-Caffeoylshikimic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	
42	3-*O*-p-Coumaroylquinic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	9945785
43	4-*O*-p-Coumaroylquinic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	101639422
44	Ethyl-3,5-di-*O*-Caffeoylquinate				Flower buds	Distilled water	1	Zhang et al. (2016)	
45	p-Coumaroyl-caffeoylquinic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	
46	Methyl 3-*O*-caffeoylquinate				Flower buds	Distilled water	1	Zhang et al. (2016)	
47	Methyl 1-*O*-caffeoylquinate				Flower buds	Distilled water	1	Zhang et al. (2016)	
48	Methyl 4-*O*-caffeoylquinate				Flower buds	Distilled water	1	Zhang et al. (2016)	
49	3-Feruloyl-4-caffeoylquinic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	91617958

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
50	3-Caffeoyl-4-feruloylquinic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	131752147
51	3-Feruloyl-5-caffeoylquinic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	101710864
52	3-Caffeoyl-5-feruloylquinic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	101710863
53	4-Feruloyl-5-caffeoylquinic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	9936820
54	4-Caffeoyl-5-feruloylquinic acid				Flower buds	Distilled water	1	Zhang et al. (2016)	92135801
55	Methyl 1,3-di-*O*-caffeoylquinate				Flower buds	Distilled water	1	Zhang et al. (2016)	
56	Methyl-3,4-di-*O*-caffeoylquinate				Flower buds	Distilled water	1, 2	Zhang et al. (2016), Guan et al. (2011)	131752148
57	Methyl-3,5-di-*O*-caffeoylquinate				Flower buds	Distilled water	1, 2	Zhang et al. (2016), Guan et al. (2011)	10075681
58	Methyl-1,4-di-*O*-caffeoylquinate				Flower buds	Distilled water	1	Zhang et al. (2016)	
59	Methyl-4,5-di-*O*-caffeoylquinate				Flower buds	Distilled water	1	Zhang et al. (2016)	
60	Methyl-1,5-di-*O*-caffeoylquinate				Flower buds	Distilled water	1	Zhang et al. (2016)	
61	Ethyl-3,4-di-*O*-caffeoylquinate				Flower buds	Distilled water	1	Zhang et al. (2016)	10554540
Cinnamic acids derivatives common for JYH and SYH									
62	Caffeic acid	Flowers	Methanol	Choi et al. (2007)	Flower buds	Ethyl acetate	4	Chai et al. (2004b)	689043
63	3-*O*-Feruloylquinic acid	Leaves/ Flowers/ Stems	70% methanol	Iwahashi et al. (1986)	Flower buds	Distilled water	1	Zhang et al. (2016)	10133609
64	4-*O*-Feruloylquinic acid	Flowers/Flower buds	Ethanol	Institute (1975)	Flower buds	Distilled water	1	Zhang et al. (2016)	4635494

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
65	5-*O*-Feruloylquinic acid	Unknown	Unknown	Iwahashi et al. (1986)	Flower buds	Distilled water	1	Zhang et al. (2016)	9799386
66	1-*O*-Caffeoylquinic acid	Unknown	Unknown	Chang and Hsu (1992)	Flower buds	n-butyl alcohol	1	Xu et al. (2006)	131751066
67	Trans-Cinnamic acid	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)	Flowers/Flower buds	Ethyl acetate	4	Wen et al. (2015)	444539
68	Trans-Ferulic acid	Whole plant	95% ethanol	Jeong et al. (2015)	Flowers/Flower buds	Ethyl acetate	3	Yao et al. (2014)	445858
Cinnamic acids derivatives only for JYH									
69	Caffeic acid methyl ester	Unknown	Unknown	Chang and Hsu (1992)					689075
70	Methyl 4-caffeoylquinate	Flowers/Flower buds	Distilled water	Yu et al. (2015b)					71720840
71	Ethyl cinnamate	Flower buds	95% ethanol	Jiang (2015)					637758
72	Caffeoylglycerol	Leaves/ Flowers/ Stems	70% methanol	Seo et al. (2012)					129728050
73	Methyl 4-*O*-β-D-glucopyranosyl caffeate	Flowers/Flower buds	Distilled water	Yu et al. (2015b)					
74	Caffeic acid ethyl ester	Flower buds	95% ethanol	Jiang (2015)					5317238
75	4-Hydroxycinnamic acid	Flower buds/ Leaves	Acetone	Feng et al. (2011), Wang (2013)					637542
76	Methyl 4-hydroxycinnamate	Flower buds	Acetone	Feng et al. (2011)					5319562
77	Isoferulic acid	Leaves	Ethanol	Wang (2013)					736186
78	3-(3,4-Dihydroxyphenyl) propionic acid	Flower buds	Acetone	Feng et al. (2011)					348154
Cinnamic acids derivatives only for SYH									
79	1-*O*-Dimethoxycinnamoylquinic				Flower buds	Distilled water	1	Zhang et al. (2016)	
80	3-*O*-Dimethoxycinnamoylquinic				Flower buds	Distilled water	1	Zhang et al. (2016)	
81	4-*O*-Dimethoxycinnamoylquinic				Flower buds	Distilled water	1	Zhang et al. (2016)	

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
Benzoic acids derivatives common for JYH and SYH									
82	2,5-Dihydroxybenzoic acid-5-*O*-β-D-glucopyranoside	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)	Flowers/Flower buds	Ethyl acetate	4	Wen et al. (2015)	
Benzoic acids derivatives only for JYH									
83	Vanillic acid	Flower buds	Ethanol	Lee et al. (2010a)					8468
84	Vanillic acid 4-*O*-β-D-(6-*O*-benzoyl glucopyranoside)	Flower buds	Ethanol	Lee et al. (2010a)					
85	Vanillic acid-4-*O*-β-D-(6-*O*-benzoyl pyranoside)	Flower buds	Ethanol	Lee et al. (2010a)					
86	Protocatechuic acid	Flowers	Methanol	Choi et al. (2007)					528594
87	4-Hydroxybenzoic acid	Flower buds	Ethanol	Li and Li (2005)					135
Flavonoids									
Flavones common for JYH and SYH									
88	Cynaroside	Flower buds	Ethyl acetate	Shuang-Cheng (2006)	Flower buds	Methanol	1, 2, 3, 4	Zhang et al. (2015)	44258205
89	Luteolin	Flowers	Methanol	Choi et al. (2007)	Flower buds	Ethyl acetate	4	Chai et al. (2004a)	5280445
90	Chrysoeriol 7-*O*-neohesperidoside	Flowers	Methanol	Choi et al. (2007)	Flower buds	n-butyl alcohol	4	Chai et al. (2004a)	44593486
91	Chrysoeriol 7-*O*-glucoside	Flowers	Methanol	Choi et al. (2007)	Flower buds	Ethyl acetate	1	Jia et al. (2008)	11294177
92	Lonicerin	Whole plant	n-butanol	Lee et al. (1995)	Flower buds	Petroleum ether	1, 3, 4	Chai et al. (2004c), Chen et al. (2007)	5282152
93	Tricin	Flower buds	n-butyl alcohol	Chai et al. (2004a)	Flower buds	n-butyl alcohol	4	Chai et al. (2004a)	5281702
94	Tricin 7-*O*-glucoside	Flower buds	Unknown	Ren et al. (2008)	Flower buds	n-butyl alcohol	4	Chai et al. (2004a)	44258267
95	Tricin 7-*O*-neohesperidoside	Flower buds	n-butyl alcohol	Huang et al. (2005)	Flower buds	n-butyl alcohol	4	Chai et al. (2004a)	44258269
Flavones only for JYH									
96	Chrysoeriol	Dried flowers	Methanol	Choi et al. (2007)					5280666
97	Rhoifolin	Aerial parts	Methanol	Son et al. (1992)					5282150
98	Flavoyadorinin B	Flower buds	Ethanol	Lee et al. (2010a)					14376376

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
99	Cupressuflavone	Unknown	Unknown	Choi et al. (2007)					5281609
100	Diosmetin	Unknown	Unknown	Choi et al. (2007)					5281612
101	5,3′-Dimethoxyluteolin	Flower buds	Acetone	Feng et al. (2011)					
102	5-Hydroxy-7,4′-dimethoxyflavone	Flower buds	Petroleum ether	Xing et al. (2002)					
103	Luteolin 7-*O*-β-D-galactoside	Flowers	Methanol	Choi et al. (2007)					5488493
104	Luteolin 3′-rhamnoside	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					44258072)
105	Chrysin	Leaves	80% methanol	Kumar et al. (2005)					5281607
106	Diosmetin 7-*O*-β-D-glucoside	Leaves	Ethanol	Wang (2013)					11016019
107	Apigenin	Aerial parts	Ethyl acetate	Zhang et al. (2006)					5280443
108	Apigenin-7-*O*-α-L-rhamnopyranoside	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					
109	Corymbosin	Flowers/Flower buds	Alcohol	Huang et al. (1996)					10970376
110	5-Hydroxy-3′,4′,7-Trimethoxylflavone	Flowers/Flower buds	Alcohol	Huang et al. (1996)					5272653
111	Ochnaflavone	Aerial parts	Ethyl acetate	Son et al. (1992)					5492110
112	Ochnaflavone 4′-*O*-methylether	Aerial parts	Ethyl acetate	Son et al. (1992)					
113	5,3′-Dimethoxy luteolin	Flower buds	50% aqueous acetone	Feng et al. (2011)					
114	Luteolin-5-*O*-β-D-glucopyranoside	Flower buds	50% aqueous acetone	Feng et al. (2011)					5317471
115	5-Hydroxy-6,7,8,4′-tetramethoxy flavone	Flower buds	95% ethanol	Jiang (2015)					
116	5-Hydroxy-7,4′-dimethoxyflavone	Flower buds	Ethyl acetate	Xing et al. (2002)					
117	5-Hydroxy-7,3′,4′,5′-tetramethoxyflavone	Flower buds	Ethyl acetate	Xing et al. (2002)					
118	5,7,3′,4′,5′-pentamethoxyflavone	Flowers/Flower buds	Ethyl acetate	Cui et al. (2012)					493376
119	5,4′-Dihydroxy3′,5′-dimethoxy-7-*O*-β-D-glucoxy flavone	Flowers/Flower buds	30% ethanol	Zhen (2010)					

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
120	Luteolin *O*-dihexoside	Leaves/ Flowers/ Stems	70% methanol	Seo et al. (2012)					
121	Apigenin 7-*O*-hexoside	Leaves/ Flowers/ Stems	70% methanol	Seo et al. (2012)					
122	Apigenin 7-*O*-rutinoside	Leaves/ Flowers/ Stems	70% methanol	Seo et al. (2012)					5377847
123	Trihydroxymethoxyflavone	Leaves/ Flowers/ Stems	70% methanol	Seo et al. (2012)					
Flavone only for SYH									
124	Chrysoeriol-7-*O*-xyloside				Flower buds	n-butanol	1	Hu et al. (2016)	
Flavonols common for JYH and SYH									
125	Rutin	Unknown	Unknown	Chang and Hsu (1992)	Flower buds	n-butanol	1, 4	Chen et al. (2006), Chai et al. (2004b)	5280805
126	Quercetin	Aerial parts	Methanol	Son et al. (1992)	Flower buds	Ethyl acetate	3, 4	Chai et al. (2004c), Chai et al. (2004a)	5280343
127	Astragalin	Aerial parts	Methanol	Son et al. (1992)	Unknown	Unknown	Unknown	Chen et al. (2006)	5282102
128	Isoquercitrin	Aerial parts	Methanol	Son et al. (1992)	Flower buds	Ethyl acetate	1	Jia et al. (2008)	5280804
129	Isorhamnetin 3-*O*-glucoside	Flowers	Methanol	Choi et al. (2007)	Flower buds	n-butyl alcohol	1	Chen et al. (2008a)	5318645
130	Hyperoside	Flower buds	Ethyl acetate	Ni (2017)	Flower buds	Methanol	1, 3, 4	Huang et al. (2005)	5281643
Flavonols only for JYH									
131	3-Methoxyluteolin	Flower buds	Acetone	Feng et al. (2011)					
132	Isorhamnetin 3-*O*-rutinoside	Flowers	Unknown	Wang (2010)					5481663
133	Kaempferol 3-*O*-β-D-rutinoside	Flower buds	Unknown	Wang (2010)					5318767
134	Kaempferol 3-*O*-hexoside	Flower buds	Ethyl acetate	Ni (2017)					

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
135	Quercetin-7-*O*-β-D-glucopyranoside	Flowers/Flower buds	n-butyl alcohol	Chen et al. (2010b)					5282160
136	Quercetin 3-*O*-hexoside	Leaves/ Flowers/ Stems	70% methanol	Seo et al. (2012)					5378597
Flavonol only for SYH									
137	Kaempferol				Flowers/Flower buds	Ethyl acetate	3	Yao et al. (2014)	5280863
Flavonolignan only for JYH									
138	Hydnocarpin	Aerial parts	Methanol	Son et al. (1992)					5489114
Flavanone only for JYH									
139	Eriodictyol	Aerial parts	Ethyl acetate	Zhang et al. (2006)					440735
Biflavonoids only for JYH									
140	3′-*O*-Methyl loniflavone[5,5″,7, 7″-tetrahydroxy 3′-methoxy 4′,4‴-biflavonyl ether	Leaves	80% methanol	Kumar et al. (2005)					
141	Loniflavone [5,5″,7,7″,3′-pentahydroxy 4′,4‴-biflavonyl ether	Leaves	80% methanol	Kumar et al. (2005)					
Iridoids									
142	Loganin	Flowers	Butanol	Tomassini et al. (1995)	Flowers/Flower buds	Ethyl acetate	3	Yao et al. (2014)	87691
143	Sweroside	Flowers	Butanol	Tomassini et al. (1995)	Flowers/Flower buds	50% methanol	1, 2, 3, 4	Chen et al. (2007), Zhang et al. (2015)	161036
144	Secologanoside	Flower buds	Distilled water	Song (2008)	Flower buds	30% ethanol	1	Chen et al. (2012b)	14136853
145	Ethyl secologanoside	Flower buds	75% ethanol	Liu et al. (2015)	Flower buds	Methanol	1	Liu et al. (2012)	
146	Centauroside	Leaves/Flowers buds/Stems	70% ethanol	Lee et al. (2010b), Machida et al. (2003)	Flower buds	50% methanol	3	Chen et al. (2007)	6440698
147	7-Epiloganin	Flower buds	Ethanol	Li and Li (2005)	Flower buds	Ethyl acetate	3	Li et al. (2003)	443343

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
148	Secoxyloganin	Flower buds	Ethyl acetate	Ma et al. (2006)	Flower buds	Ethyl acetate	1, 3, 4	Chen et al. (2007), Lee (2004)	162868
149	Secologanic acid	Flower buds	Ethyl acetate	Ni (2017)					5321213
150	Secologanin	Flowers	Butanol	Tomassini et al. (1995)					161276
151	7-Epi vogeloside	Flowers/Flower buds	Chloroform	Bi et al. (2007)					
152	Morroniside	Flower buds	Unknown	Kakuda et al. (2000)					11304302
153	Loganin aglycone	Roots	95% ethanol	Jin-qian et al. (2016)					
154	7-Dimethyl-secologanoside	Leaves	Ethanol	Wang (2013)					
155	Secologanin dimethyl acetal	Leaves/Flower buds	Ethyl acetate	Machida and Asano (1995), Lee et al. (2010b)					157140
156	7-*O*-Butylsecologanic acid	Flowers	Butanol	Tomassini et al. (1995)					101687692
157	Secologanin dibutylacetal	Flowers	Butanol	Tomassini et al. (1995)					
158	Kingiside	Flower buds	Unknown	Kakuda et al. (2000)					12304884
159	Vogeloside	Flower buds	n-butyl alcohol	Song et al. (2008)					14192588
160	Epi-vogeloside	Flower buds	n-butyl alcohol	Song et al. (2008)					14192590
161	Ketologanin	Flower buds	Distilled water	Song (2008)					
162	7α-Morroniside	Flower buds	Distilled water	Song (2008)					
163	7β-Morroniside	Flower buds	Distilled water	Song (2008)					
164	Lonijaposide A	Flower buds	Distilled water	Liu et al. (2015)					24879108
165	Lonijaposide A1	Flowers	Methanol	Kumar et al. (2006)					
166	Lonijaposide A2	Flowers	Methanol	Kumar et al. (2006)					
167	Lonijaposide A3	Flowers	Methanol	Kumar et al. (2006)					

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
168	Lonijaposide A4	Flowers	Methanol	Kumar et al. (2006)					
169	Lonijaposide B	Flower buds	Distilled water	Liu et al. (2015)					24879110
170	Lonijaposide B1	Flowers	Methanol	Kumar et al. (2006)					
171	Lonijaposide B2	Flowers	Methanol	Kumar et al. (2006)					
172	Lonijaposide C	Flower buds	Distilled water	Liu et al. (2015)					24879106
173	Lonijaposide D	Flower buds	Distilled water	Song (2008)					56599664
174	Lonijaposide E	Flower buds	Distilled water	Song (2008)					56599666
175	Lonijaposide F	Flower buds	Distilled water	Song (2008)					56599668
176	Lonijaposide G	Flower buds	Distilled water	Song (2008)					56599669
177	Lonijaposide H	Flower buds	Distilled water	Song (2008)					56599868
178	Lonijaposide I	Flower buds	Distilled water	Song (2008)					56598336
179	Lonijaposide J	Flower buds	Distilled water	Song (2008)					56599869
180	Lonijaposide K	Flower buds	Distilled water	Song (2008)					56599871
181	Lonijaposide L	Flower buds	Distilled water	Song (2008)					56599872
182	L-Phenylalaninosecologanin	Stems/leaves	Methanol	Machida et al. (2003)					101189142
183	7-*O*-(4-β-D-Glucopyranosyloxy-3-methoxy-benzoyl) secologanolic acid	Stems/leaves	Methanol	Machida et al. (2003)					
184	6′-*O*-(7α-Hydroxyswerosyloxy) loganin	Stems/leaves	Methanol	Machida et al. (2003)					
185	(E)-Aldosecologanin	Stems/leaves	Methanol	Machida et al. (2003)					45783101
186	Loniceracetalide A	Flower buds	Ethyl acetate	Kakuda et al. (2000)					
187	Loniceracetalide B	Flower buds	Ethyl acetate	Kakuda et al. (2000)					
188	8-Epiloganin	Flower buds	Boiling water	Liu et al. (2015)					10548420
189	Loganic acid	Flower buds	Boiling water	Liu et al. (2015)					89640
190	8-Epiloganic acid	Flower buds	Boiling water	Liu et al. (2015)					158144

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
191	Secologanoside-7-methyl ester	Flower buds	Ethyl acetate	Kakuda et al. (2000)					14038297
192	8-Epikingiside	Flower buds	Boiling water	Liu et al. (2015)					12304886
193	7-Hydroxy-methyl-vogeloside	Unknown	Unknown	Tian (2007)					
194	Loniaceticiridoside	Flower buds	Distilled water	Song et al. (2015a)					
195	Lonimalondialiridoside	Flower buds	Distilled water	Song et al. (2015a)					
196	6′-*O*-Acetylvogeloside	Flowers/Flower buds	95% ethanol	Xu et al. (2012)					
197	6′-*O*-Acetylsecoxyloganin	Flowers/Flower buds	95% ethanol	Xu et al. (2012)					
198	Adinoside A	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					11144737
199	Stryspinoside	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					76331806
200	Dimethylsecologanoside	Flower buds	Ethyl acetate	Ma et al. (2006)					14105070
201	Loniphenyruviridoside A	Unknown	Unknown	Yu et al. (2011)					57395335
202	Loniphenyruviridoside B	Unknown	Unknown	Yu et al. (2011)					56598467
203	Loniphenyruviridoside C	Unknown	Unknown	Yu et al. (2011)					57398873
204	Loniphenyruviridoside D	Unknown	Unknown	Yu et al. (2011)					56598469
205	Loniceranan A	Dried flower buds	75% ethanol	Liu et al. (2015)					
206	Loniceranan B	Dried flower buds	75% ethanol	Liu et al. (2015)					
207	Loniceranan C	Dried flower buds	75% ethanol	Liu et al. (2015)					
208	Demethylsecologanol	Dried flower buds	75% ethanol	Liu et al. (2015)					
209	Harpagide	Dried flower buds	75% ethanol	Liu et al. (2015)					10044294
210	Harpagoside	Dried flower buds	75% ethanol	Liu et al. (2015)					5281542
211	6″-*O*-β-Glucopyranosylharpagoside	Dried flower buds	75% ethanol	Liu et al. (2015)					

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
212	(7β)-7-*O*-Methyl morroniside	Dried flower buds	75% ethanol	Liu et al. (2015)					
213	Serinosecologanin	Flower buds	Distilled water	Song et al. (2014)					
214	Threoninosecologanin	Flower buds	Distilled water	Song et al. (2014)					
215	Lonijapospiroside A	Flower buds	70% ethanol	Zheng et al. (2012)					
216	L-Phenylalaninosecologanin B	Flower buds	70% ethanol	Zheng et al. (2012)					
217	L-Phenylalaninosecologanin C	Flower buds	70% ethanol	Zheng et al. (2012)					
218	Dehydroprolinoylloganin A	Flower buds	70% ethanol	Zheng et al. (2012)					
219	Lonijaposide M	Unknown	Unknown	Yu et al. (2011)					56599874
220	Lonijaposide N	Unknown	Unknown	Yu et al. (2011)					56600069
221	Lonijaposide O	Flower buds	Distilled water	Yu et al. (2013)					
222	Lonijaposide P	Flower buds	Distilled water	Yu et al. (2013)					
223	Lonijaposide Q	Flower buds	Distilled water	Yu et al. (2013)					
224	Lonijaposide R	Flower buds	Distilled water	Yu et al. (2013)					
225	Lonijaposide S	Flower buds	Distilled water	Yu et al. (2013)					
226	Lonijaposide T	Flower buds	Distilled water	Yu et al. (2013)					
227	Lonijaposide U	Flower buds	Distilled water	Yu et al. (2013)					
228	Lonijaposide V	Flower buds	Distilled water	Yu et al. (2013)					
229	Lonijaposide W	Flower buds	Distilled water	Yu et al. (2013)					
230	7-*O*-Ethyl sweroside	Flower buds	Methanol	Song et al. (2006)					
231	Secoxyloganin 7-butyl ester	Flower buds	Methanol	Song et al. (2006)					
232	Grandifloroside	Roots	95% ethanol	Jin-qian et al. (2016)					20056012
233	7-Dehydrologanin	Flower buds	70% ethanol	Lee et al. (2010b)					443349
234	6′-*O*-α-L-Arabinopyranosyl demethylsecologanol				Flower buds	Methanol	1	Liu et al. (2012)	
Saponins									
235	α-Hederin	Flower buds	Ethanol	Chen et al. (2000)	Unknown	Unknown	Unknown	Chen et al. (2000)	73296
236	Loniceroside A	Aerial parts	Methanol	Ho Son et al. (1994)	Flowers/Flower buds	Ethyl acetate	Unknown	Lin et al. (2008)	
237	Loniceroside B	Aerial parts	Methanol	Ho Son et al. (1994)	Flowers/Flower buds	Ethyl acetate	Unknown	Lin et al. (2008)	

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
238	Loniceroside C	Aerial parts	Butanol	Kwak et al. (2003)	Flowers/Flower buds	Ethyl acetate	Unknown	Lin et al. (2008)	
239	Loniceroside D	Flowers/Flower buds	Ethanol	Lin et al. (2008)	Flowers/Flower buds	Ethyl acetate	Unknown	Lin et al. (2008)	
240	Loniceroside E	Flowers/Flower buds	Ethanol	Lin et al. (2008)	Flowers/Flower buds	Ethyl acetate	Unknown	Lin et al. (2008)	
241	3-*O*-α-L-Arabinopyranosyl-28-*O*-[β-D-glucopyranosyl(1 → 6)-β-D-glucopyranosyl] oleanolic acid	Aerial parts	Methanol	Kawai et al. (1988)	Flower buds	n-butyl alcohol	1	Chen et al. (2006)	
242	3-*O*-[α-L-Rahmnopyranosyl(1 → 2)-α-L-arabinopyranosyl]-28-*O*-[β-D-glucopyranosyl(1 → 6)-β-D-glucopyranosyl] oleanolic acid	Aerial parts	Boiling water	Kawai et al. (1988)	Flower buds	Ethyl acetate	1	Jia et al. (2007)	
243	Hederagenin 3-*O*-α-L-arabinopyranoside	Flowers	Ethyl acetate	Choi et al. (2007)					
244	Hederagenin	Whole plant	Butanol	Yu et al. (2015a)					73299
245	Oleanolic acid	Flower buds	Unknown	Wang (2010)					10494
246	Ursolic acid	Flowers/Flower buds	95% ethanol	Xu et al. (2012)					64945
247	Nortirucallane A	Flowers/Flower buds	80% ethanol	Wang et al. (2017b)					
248	Saponin 1	Flower buds	Methanol	Qi et al. (2009)					
249	Saponin 4	Flower buds	Methanol	Qi et al. (2009)					482163
250	Daucosterol	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					5742590
251	Oleanolic acid 28-α-*O*-l-rhamnopyranosyl-(1 → 2)-[β-D-xylopyranosyl(1 → 6)]-β-D-glucopyranosyol ester	Flowers	Methanol	Choi et al. (2007)					

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
252	Hederagenin-3-*O*-α-L-rhamnopyranosyl1 → 2-α-L-arabinopyranoside	Flower buds	Ethanol	Chen et al. (2000)					
253	Hederagenin-3-*O*-α-L-rhamnopyranosyl (1 → 2)-α-L-arabinopyranoside	Flower buds	Ethanol	Chen et al. (2000)					
254	3-*O*-[α-L-Rahmnopyranosyl(1 → 2) -α-L-arabinopyranosyl]-28-*O*-β-D-glucopyranosyl hederagenin	Aerial parts	Methanol	Kawai et al. (1988)					
255	3-*O*-[α-L-Rahmnopyranosyl(1 → 2) -α-L-arabinopyranosyl]-28-*O*-[6-acetyl -β-D-glucopyranosyl(1 → 6)-β-D-glucopyranosyl] hederagenin	Aerial parts	Boiling water	Kawai et al. (1988)					
256	3-*O*-α-L-Arabinopyranosy hederagenin 28-*O*-α-D-rahmnopyranosyl(1 → 2) [β-D-xylpyranosyl(1 → 6)-β-D-glucopyranosyl ester	Flower buds	95% ethanol	Lou et al. (1996)					
257	3-*O*-α-L-Rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosy hederagenin 28-*O*-β-D-xylpyranosyl(1 → 6)-β-D-glucopyranosyl ester	Flower buds	95% ethanol	Lou et al. (1996)					
258	3-*O*-α-L-Rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosy hederagenin 28-*O*-α-D-Rhamnopyranosyl(1 → 2) [β-D-xylpyranosyl(1 → 6)-β-D-glucopyranosylester	Flower buds	95% ethanol	Lou et al. (1996)					

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
259	3-*O*-β-D-Glucopyranosyl-(1 → 4) -β-L-glucopyranosyl(1 → 3) -α-L-rhamnopyranosyl(1 → 2) -α-L-arabinopyranosy hederagenin28-*O*-β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranosyl ester	Flower buds	Ethanol	Chen et al. (2000)					
260	3-*O*-α-L-Rhamnopyranosyl-(1 → 2) -α-L-arabinopyranosy hederagenin 28-*O*-β-D-glucopyranosyl(1 → 6) -β-D-glucopyranosyl ester	Flower buds	Ethanol	Chen et al. (2000)					
261	3-*O*-β-D-Glucopyranosyl-(1 → 3) -α-L-rhamnopyranosyl(1 → 2) -α-L-arabinopyranosyl hederagenin 28-*O*-β-D-glucopyranosyl-(1 → 6) -β-D-glucopyranosyl ester	Flower buds	Ethanol	Chen et al. (2000)					
262	3-*O*-β-D-Glucopyranosyl-(1 → 2) -α-L-arabinopyranosyl oleanolic acid-28-*O*-β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranoside	Unknown	Unknown	Xing et al. (2002)					
263	3-*O*-β-D-Glucopyranosyl-(1 → 4)-β-D-glucopyranosyl(1 → 3)-α-L-rhamnopyranosyl(1 → 2) -α-L-arabinopyranosy hederagenin 28-*O*-β-D-glucopyranosyl-(1 → 6) -β-D-glucopyranosyl ester	Flower buds	Ethanol	Chen et al. (2000)					
264	3-*O*-α-L-Rhamnopyranosyl-(1 → 2) -α-L-arabinopyranosy hederagenin 28-*O*-β-D-xylopyranosyl(1 → 6) -β-D-glucopyranosyl ester	Flower buds	Ethanol	Chen et al. (2000)					

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
265	Macranthoidin A				Flowers/Flower	Ethanol	1, 2, 3, 4	Ren et al. (2008), Mao et al. (1993)	14564503
266	Macranthoidin B				Flowers/Flower	Ethanol	1, 2, 3, 4	Ren et al. (2008), Mao et al. (1993)	119025667
267	Macranthoside B				Flowers/Flower	Ethanol	1, 3, 4	Chai et al. (2005), Mao et al. (1993)	135396862
268	Macranthoside A				Flowers/Flower	Ethanol	1, 3, 4	Chai et al. (2005), Mao et al. (1993)	176534
269	Dipsacoside B				Flowers/Flower	Ethanol	1, 2, 3, 4	Ren et al. (2008), Mao et al. (1993)	21627940
270	Dipsacoside VI				Unknown	Unknown	Unknown	Huang et al. (2017)	
271	Hederagenin-3-*O*-α-L-arabinopyranosyl (2 → 1)-*O*-α-L-rhamnopyranoside				Flowers	Methanol	1, 3, 4	Chai et al. (2005)	
272	Hederagenin-28-*O*-β-D-glucopyranosyl (6 → 1)-*O*-β-D-glucopyranosyl ester				Flower buds	50% methanol	1	Chen et al. (2007)	
273	Thalictoside VI				Flower buds	70% ethanol	1	Chen et al. (2015a)	23815408
274	Asiatic acid				Flower buds	70% ethanol	1	Chen et al. (2015a)	119034
275	Leiyemudanoside A				Flower buds	Methanol	1	Liu et al. (2013)	
276	Lonimacranthoide I				Flower buds	50% ethanol	1	Chen et al. (2012a)	
277	Lonimacranthoide II				Flower buds	50% ethanol	1	Chen et al. (2012a)	
278	Lonimacranthoide III				Flower buds	50% ethanol	1	Chen et al. (2008b)	
279	Lonimacranthoide IV				Flower buds	Ethanol	1	Yu et al. (2012)	

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
280	Lonimacranthoide V				Flower buds	Ethanol	1	Yu et al. (2012)	
281	Lonimacranthoide VI				Flower buds	Unknown	1	Guan et al. (2014a)	
282	2α, 24-dihydroxy-23-nor-ursolic acid				Flower buds	70% ethanol	1	Chen et al. (2015a)	
283	2α, 4α-dihydroxy-23-nor-ursolic acid				Flower buds	70% ethanol	1	Chen et al. (2015a)	
284	Akebia saponin D				Flower buds	70% ethanol	1	Chen et al. (2015a)	14284436
285	3β-*O*-β-D-Glucopyranosyl-(1 → 3) -α-L-rhamnopyranosyl-(1 → 2)- α- L-arabinopyranosyl-hederagenin-28-*O*-β-D-glucopyranosyl ester				Flower buds	70% ethanol	1	Chen et al. (2015a)	
286	3β-*O*-α-L-Rhamnopyranosyl- (1 → 2)-α- L-arabinopyranosyl-28-*O*-β-D- glucopyranosyl-(1 → 6)-β-D- glucopyranosyl oleanolic acid				Flower buds	70% ethanol	1	Chen et al. (2015a)	
287	3-*O*-β-D-Glucopyranosyl-(1 → 4)- β-D-glucopyranosyl-(1 → 3)- α-L-rhamnopyranosyl-(1 → 2) -α-L-arabinopyranosyl-23- hydroxyolean-18-en-28-oic acid *O*-β-D-glucopyranosyl- (1 → 6)-β-D-glucopyranosyl ester				Flower buds	Methanol	1	Liu et al. (2013)	
288	3-*O*-β-D-Glucopyranosyl-(1 → 4) -β-D-glucopyranosyl-(1 → 3) -α-L-rhamnopyranosyl-(1 → 2) -α-L-arabinopyranosyl]-23- hydroxyolean lup-(2029)- en-28-oic acid *O*-β-D- glucopyranosyl-(1 → 6) -β-D-glucopyranosyl ester				Flower buds	Methanol	1	Liu et al. (2013)	

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
289	3-*O*-β-D-Glucopyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-β-D-xylopyranosyl]-23-hydroxyolean hederagenin *O*-β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranosyl ester				Flower buds	Methanol	1	Liu et al. (2013)	
Essential oils									
290	9,12,15-Octadecatrienoic acid methyl ester	Flowers	Absolute ether	Wang et al. (2009c)	Flower buds	Distilled water	1	Wu et al. (2015a)	9316
291	Hexadecane	Flowers	Absolute ether	Wang et al. (2009c)	Flower buds	Ethyl acetate	1	Wu et al. (2015a)	11006
292	Nonadecane	Flowers	Absolute ether	Wang et al. (2009c)	Flower buds	Distilled water	1	Wu et al. (2015a)	12401
293	Dibutyl phthalate	Flowers/Flower buds	Absolute ether	Yang and Zhao (2007)	Flower buds	Distilled water	1	Wu et al. (2015a)	3026
294	Hexadecanoic acid methyl ester	Flowers	Absolute ether	Wang et al. (2009c)	Flower buds	Distilled water	1	Wang et al. (1999)	8181
295	Linalool	Flowers/Flower buds	Absolute ether	Yang and Zhao (2006)	Flower buds	Ethyl acetate	1	Tong et al. (2005)	6549
296	Octadecanal	Flowers	Absolute ether	Wang et al. (2009c)					12533
297	Phytol	Flowers	Absolute ether	Wang et al. (2009c)					5280435
298	α-Terpineol	Flowers	Absolute ether	Wang et al. (2009c)					17100
299	5-(Prop-2-enoyloxy)pentadecane	Flowers	Absolute ether	Wang et al. (2009c)					543288
300	Eicosane	Flowers	Absolute ether	Wang et al. (2009c)					8222
301	Triacontane	Flowers	Absolute ether	Wang et al. (2009c)					12535
302	2,6,10-Trimethyltetradecane	Flowers	Absolute ether	Wang et al. (2009c)					85785
303	Octadecane	Flowers	Absolute ether	Wang et al. (2009c)					11635

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
304	Heptadecane	Flowers	Absolute ether	Wang et al. (2009c)					12398
305	Pentadecane	Flowers	Absolute ether	Wang et al. (2009c)					12391
306	Hexane	Flowers	Absolute ether	Wang et al. (2009c)					8058
307	Linalool oxide	Flowers	Absolute ether	Wang et al. (2009c)					6431477
308	Methyl linolenate	Flower buds	Distilled water	Du et al. (2015)					5319706
309	ε-Muurolene	Flower buds	Distilled water	Du et al. (2015)					520461
310	α-Curcumene	Flower buds	Distilled water	Du et al. (2015)					92139
311	Carvacrol	Flowers/Flower buds	Absolute ether	Yang and Zhao (2006)					10364
312	Farnesol	Flowers	Distilled water	Guan et al. (2014b)					445070
313	Ascorbyl dipalmitate	Flowers	Distilled water	Guan et al. (2014b)					54722209
314	Nonacosane	Flowers	Distilled water	Guan et al. (2014b)					12409
315	Benzenepropanal	Flower buds	Distilled water	Du et al. (2015)					7707
316	Ethylbenzene	Flower buds	Distilled water	Du et al. (2015)					7500
317	Linalool oxide trans	Flower buds	Distilled water	Du et al. (2015)					6432254
318	Isophytol	Flower buds	Distilled water	Du et al. (2015)					10453
319	Cyclohexanol	Flower buds	Distilled water	Du et al. (2015)					7966
320	Oxalic acid	Flower buds	Distilled water	Du et al. (2015)					971
321	Cyclohexyl isobutyl ester	Flower buds	Distilled water	Du et al. (2015)					6421303
322	(Cyclopentylmethyl)cyclohexane	Flower buds	Distilled water	Du et al. (2015)					20490
323	(Cyclohexylmethyl)benzene	Flower buds	Distilled water	Du et al. (2015)					
324	Aromadendrene	Unknown	Unknown	Wang (2010)					91354
325	Geraniol	Unknown	Unknown	Wang (2010)					637566
326	(Z)-Jasmone	Flowers	Hexane	Ikeda et al. (1994)					1549018
327	(Z)-Jasmin lactone	Flowers	Hexane	Zhang (2014)					
328	Methyl jasmonate	Flowers	Hexane	Zhang (2014)					5281929
329	Methyl epi-jasmonate	Flowers	Hexane	Zhang (2014)					5367719
330	Benzaldehyde	Flowers/Stems/Leaves	Distilled water	Wu et al. (2009)					240

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
331	Diethyl phthalate	Flowers/Stems/Leaves	Distilled water	Wu et al. (2009)					6781
332	Propylbenzene	Flowers	Diethyl ether	Du et al. (2009)					7668
333	Translinalool	Flowers	Diethyl ether	Du et al. (2009)					
334	Cyclohexylisooxalic ester	Flowers	Diethyl ether	Du et al. (2009)					
335	Methylcyclohexane	Flowers	Diethyl ether	Du et al. (2009)					7962
336	1-Octanol	Flowers	Absolute ether	Wang et al. (2009c)					967
337	5-Octen-1-ol	Flowers	Absolute ether	Wang et al. (2009c)					62231
338	1-Octadecanol	Flowers	Absolute ether	Wang et al. (2009c)					8221
339	Heptanal	Flowers	Absolute ether	Wang et al. (2009c)					8130
340	Octanone	Flowers	Absolute ether	Wang et al. (2009c)					8093
341	Acetic acid ethyl ester	Flowers	Absolute ether	Wang et al. (2009c)					8857
342	Benzeneacetic acid methyl ester	Flowers	Absolute ether	Wang et al. (2009c)					7559
343	Docosanoic acid methyl ester	Flowers	Absolute ether	Wang et al. (2009c)					13584
344	Tetracosanoic acid methyl ester	Flowers	Absolute ether	Wang et al. (2009c)					75546
345	Benzyl benzoate	Flowers	Absolute ether	Wang et al. (2009c)					2345
346	6,10,14-Trimethyl-2-pentadecanol				Flower buds	Distilled water	1	Wang et al. (1999)	530418
347	Dimethyl phthalate				Flower buds	Distilled water	1	Wu et al. (2015a)	8554
348	Octadecanoic acid				Flower buds	Distilled water	1	Wu et al. (2015a)	5281
349	1,2,3-Propanetriol, monoacetate				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	33510

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
350	9,12-Octadecadien-1-ol				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	5462912
351	10-Nonadecanol				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	85611
352	Heneicosane				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	12403
353	Hexadecanoic acid butyl ester				Flower buds	Distilled water	1	Wu et al. (2015a)	8090
354	3,7,11,15-Tetramethyl-2-hexadecen-1-ol				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	5366244
355	Phenylethyl alcohol				Flower buds	Distilled water	1	Wu et al. (2015a)	6054
356	1-Hexadecanol				Flower buds	Distilled water	1	Wu et al. (2015a)	2682
357	Heptadecane,2,6,10,15-tetramethyl-3-Hydroxy-2,2,6-trimethyl-6-vinyltetrahydropyran				Flower buds	Distilled water	1	Wu et al. (2015a)	
358	Nerol				Flower buds	Distilled water	1	Wu et al. (2015a)	643820
359	Benzoic acid, 4-formyl methyl ester				Flower buds	Distilled water	1	Wu et al. (2015a)	15294
360	Undecanoic acid				Flower buds	Distilled water	1	Wu et al. (2015a)	8180
361	12,15-Octadecadienoic acid, methyl ester				Flower buds	Distilled water	1	Wu et al. (2015a)	5365571
362	9,12,15-Octadecatrienoic acid, methyl ester				Flower buds	Distilled water	1	Wu et al. (2015a)	5367462
363	9,12,15-Octadecatrien-1-ol				Flower buds	Distilled water	1	Wu et al. (2015a)	5367327
364	1-Heptacosanol				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	74822
365	Pentatriacontane				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	12413

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
366	Pentanoic acid ethyl ester				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	10882
367	Hexanoic acid				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	8892
368	Di-isobutyl phthalate				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	6782
369	2-Nonadecanone				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	69423
370	Tetracosane				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	12592
371	Octadecanoic acid butyl ester				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	31278
372	Acetic acid octadecyl ester				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	69968
373	Citronellyl isobutyrate				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	60985
374	Eicosanoic acid				Flower buds	Ethyl acetate	1	Wu et al. (2015a)	10467
Others									
Aliphatics									
375	Linoleic acid	Flower buds	Diethyl ether	Du et al. (2015)	Flower buds	Distilled water	1	Wu et al. (2015a)	5280450
376	Tetradecanoic acid	Flowers/Flower buds	Absolute ether	Wang et al. (2009c)	Flower buds	Distilled water	1	Wu et al. (2015a)	11005
377	Ethyl laurate	Flower buds	95% ethanol	Jiang (2015)					7800
378	Nonacontane	Flower buds	Unknown	Wang (2008)					18980672
379	2(E)-3-ethoxyacrylic acid	Flowers/Flower buds	Chloroform	Bi et al. (2007)					5709609
Phenols									
380	Lonicerjaponin A	Flower buds	Methanol	Kashiwada et al. (2013)					102497708
381	Lonicerjaponin B	Flower buds	Methanol	Kashiwada et al. (2013)					102497709
382	3,4-Dihydroxybenzaldehyde	Flowers/Flower buds	Alcohol	Huang et al. (1996)					8768

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
383	p-Hydroxybenzaldehyde	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					126
384	P-Hydroxy-phenol	Flower buds	Acetone	Feng et al. (2011)					785
385	1,2,4-Benzenetriol	Flower buds	Acetone	Feng et al. (2011)					10787
Nucleosides									
386	5′-*O*-Methyladenosine	Flower buds	Distilled water	Song et al. (2008)					6480505
387	Guanosine	Flower buds	Distilled water	Song et al. (2008)					135398635
388	Adenosine	Flower buds	Distilled water	Song et al. (2008)					60961
389	Uracil	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					1174
390	5-Methyluracil	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					1135
391	Guanosinyl-(3′ → 5′) -adenosine monophosphate	Flowers/Flower buds	Distilled water	Yu et al. (2015b)					
392	2′-*O*-Methyladenosine	Flowers/Flower buds	Distilled water	Yu et al. (2015b)					102213
Alkaloids									
393	Lonijaponinicotinosides A	Flower buds	Distilled water	Jiang et al. (2015)					
394	Lonijaponinicotinosides B	Flower buds	Distilled water	Jiang et al. (2015)					
395	(+)-*N*-(3-Methybutyryl-β-D-glucopyranoyl)-nicotinate	Flower buds	Distilled water	Song (2008)					
396	(+)-*N*-(3-Methybut-2-enoyl-β-D-glucopyranosyl)-nicotinate	Flower buds	Distilled water	Song (2008)					
397	6-Hydroxymethyl-3-pyridinol	Flowers/Flower buds	Distilled water	Yu et al. (2015b)					
Triterpenoids									
398	Limonin	Unknown	Unknown	Zhen (2010)					179651
Sesquiterpenoids									
399	Abscisic acid	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					5375199
Sterols									
400	β-Sitosterol	Flowers/Flower buds	Alcohol	Huang et al. (1996)					222284

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
Saccharides									
401	Sucrose	Flower buds	70% ethanol	Lee et al. (2010b)					5988
Lignans									
402	(−)-Lyoniresinol 9-*O*-β-D-glucopyranoside	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					
403	(+)-Lyoniresinol 9-*O*-β-D-glucopyranoside	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					
Aromatic glycosides									
404	(−)-2-Hydroxy-5-methoxybenzoic acid 2-*O*-β-D-(6-*O*-benzoyl-glucopyranoside)	Flower buds	Ethyl acetate	Wang et al. (2013b)					
405	(−)-4-Hydroxy-3,5-dimethoxybenzoic acid 4-*O*-β-D-(6-*O*-benzoyl) -glucopyranoside	Flower buds	Ethyl acetate	Wang et al. (2013b)					
406	(−)-E-3,5-Dimethoxyphenyl-propenoic acid 4-*O*-β-D-(6-*O*-benzoyl) -glucopyranoside	Flower buds	Ethyl acetate	Wang et al. (2013b)					
407	(−)-(7S,8R)-4-Hydroxyphenylglycerol 9-*O*-β-D-[6-*O*-(E)-4-hydroxy-3, 5-dimethoxyphenylpropenoyl] -glucopyranoside	Flower buds	Ethyl acetate	Wang et al. (2013b)					
408	(−)-(7S,8R)-(4-Hydroxyphenylglycerol9-*O*-β-D-[6-*O*-(E)-4-hydroxy-3, 5-dimethoxyphenylpropenoyl]-glucopyranoside	Flower buds	Ethyl acetate	Wang et al. (2013b)					
409	(−)-4-hydroxy-3-Methoxyphenol β-D-{6-*O*-[4-*O*-(7S,8R)-(4-hydroxy-3-methoxyphenylglycerol-8-yl)-3-methoxybenzoyl]}-glucopyranoside	Flower buds	Ethyl acetate	Wang et al. (2013b)					
410	Benzyl alcohol β-D-glucoside	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					

Table 4 continued

No.	Compound	JYH		Reference	SYH		Origins	References	PubChem CID
		Parts	Extraction		Parts	Extraction			
411	Benzyl 2-*O*-β-D-glucopyranosyl-2, 6-dihydroxy benzoate	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					
412	Gentisic acid 5-*O*-β-D-glucopyranoside	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					
413	Eugenyl β-D-glucopyranoside	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					3084296
414	Eugenyl β-D-xylopyranosyl-(1 → 6)-β-D-glucopyranoside	Flowers/Flower buds	Ethyl acetate	Wang et al. (2013a)					
Miscellaneous									
415	2-Butanol	Unknown	Unknown	Wang et al. (2009c)					6568
416	1-*O*-Methyl-myo-inositol	Flower buds	Unknown	Wang (2008)					440078
417	Syringin	Flowers/Flower buds	Distilled water	Yu et al. (2015b)					5316860
418	Coniferin	Roots	95% ethanol	Jin-qian et al. (2016)					5280372
419	5-Hydroxymethyl-2-furfural	Flowers/Flower buds	Methanol	Choi et al. (2007)					237332
420	Shuangkangsu	Flowers	Unknown	Wang (2008)					
421	Citric acid				Flowers/Flower buds	Distilled water	1	Zhang et al. (2012)	311

1—*L. macranthoides*, 2—*L. fulvotomentosa*, 3—*L. hypoglauca*, 4—*L. confusa*

Phytochemistry

Previous phytochemical studies have indicated JYH and SYH multiplicate composition, predominantly phenolic acids, flavonoids, iridoids and saponins. Both of the two herbs contain a lot of essential oils. To date, a total of 326 compounds and 148 compounds have been isolated and identified from JYH and SYH (Yang et al. 2016; Ni 2017; Lin et al. 2008; Wu et al. 2016). Compounds presenting in JYH and SYH are summarized in Table 4, and the major ones are illustrated in Figs. 2, 3, 4, 5. Moreover, the differences on contents of major compounds are exhibited in Table 5. To expound advances in pharmacological study, the bioactive compounds of JYH and SYH are reviewed in Table 6.

Phenolic acids

JYH and SYH contain similar phenolic acids that are important bioactive compounds in JYH and SYH (Duan et al. 2018). There are 16 phenolic acids presenting in both JYH and SYH, most of which are caffeic acid derivatives. According to 2015 Edition ChP, the content of chlorogenic acid (**1**, CGA) in JYH must be no less than 1.5%, while the content of CGA (**1**) in any origin of SYH must be no less than 2.0%. SYH total phenolic acids content is also higher than that of JYH (Yang et al. 2016). Four origins of SYH contain similar chlorogenic acids derivatives. May be the cause of insufficient researches of SYH, *L. macranthoides* contains more phenolic acids than the other three origins.

The antioxidative property is closely related to the structure, in particular to electron delocalization of the aromatic nucleus (Cuvelier et al. 2014). As it is widely known, a number of naturally occurring molecules known for their antioxidative potency are phenolic acids which react with the free radicals and generate a new radical stabilized by the resonance effect of the aromatic nucleus (Larson 1988). Meanwhile, the presence of a second hydroxy group in the *ortho* or *para* position of phenolic acids could increase their antioxidant capacity. A wide range of researches demonstrate that changes of antioxidant intensity are always closely associated with the variation of the contents of phenolic acids (Porter et al. 2010; Farhat et al. 2014; Ben Farhat et al. 2015).

CGA (**1**) and caffeic acid (**62**, CA) are the two most studied compounds in JYH and SYH, which have already been confirmed to possess potent activities against inflammation and oxidation via removing harmful free radicals from body in vitro and in vivo (Feng et al. 2005; Chen et al. 2010a; Sato et al. 2011).

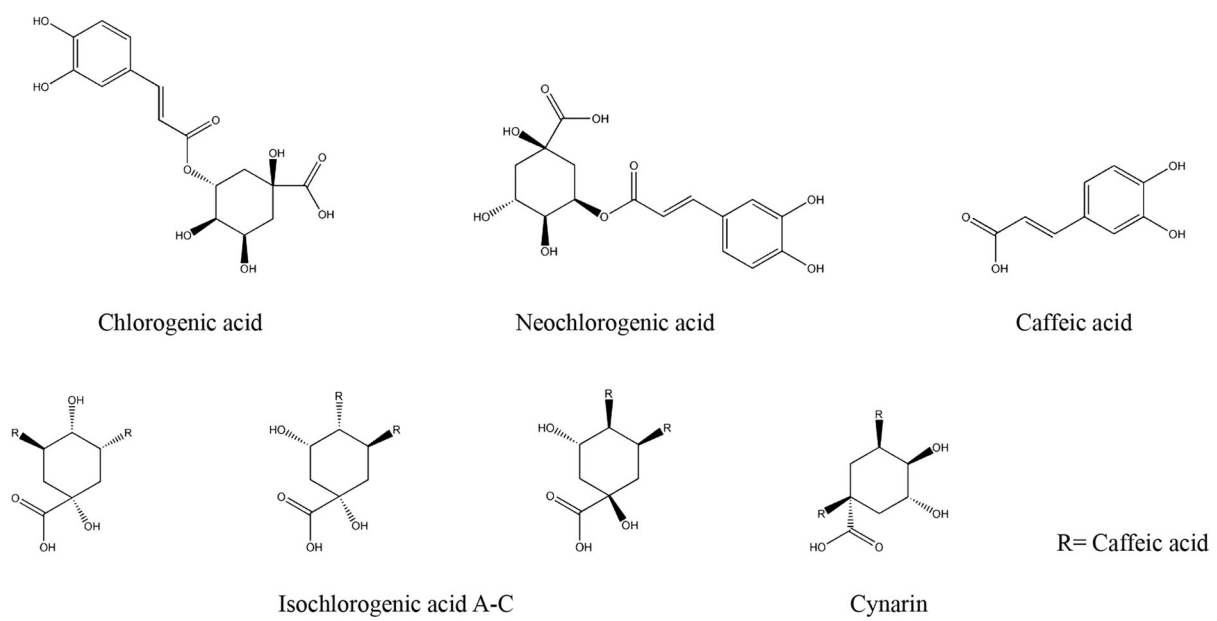


Fig. 2 The major phenolic acids presenting in both JYH and SYH

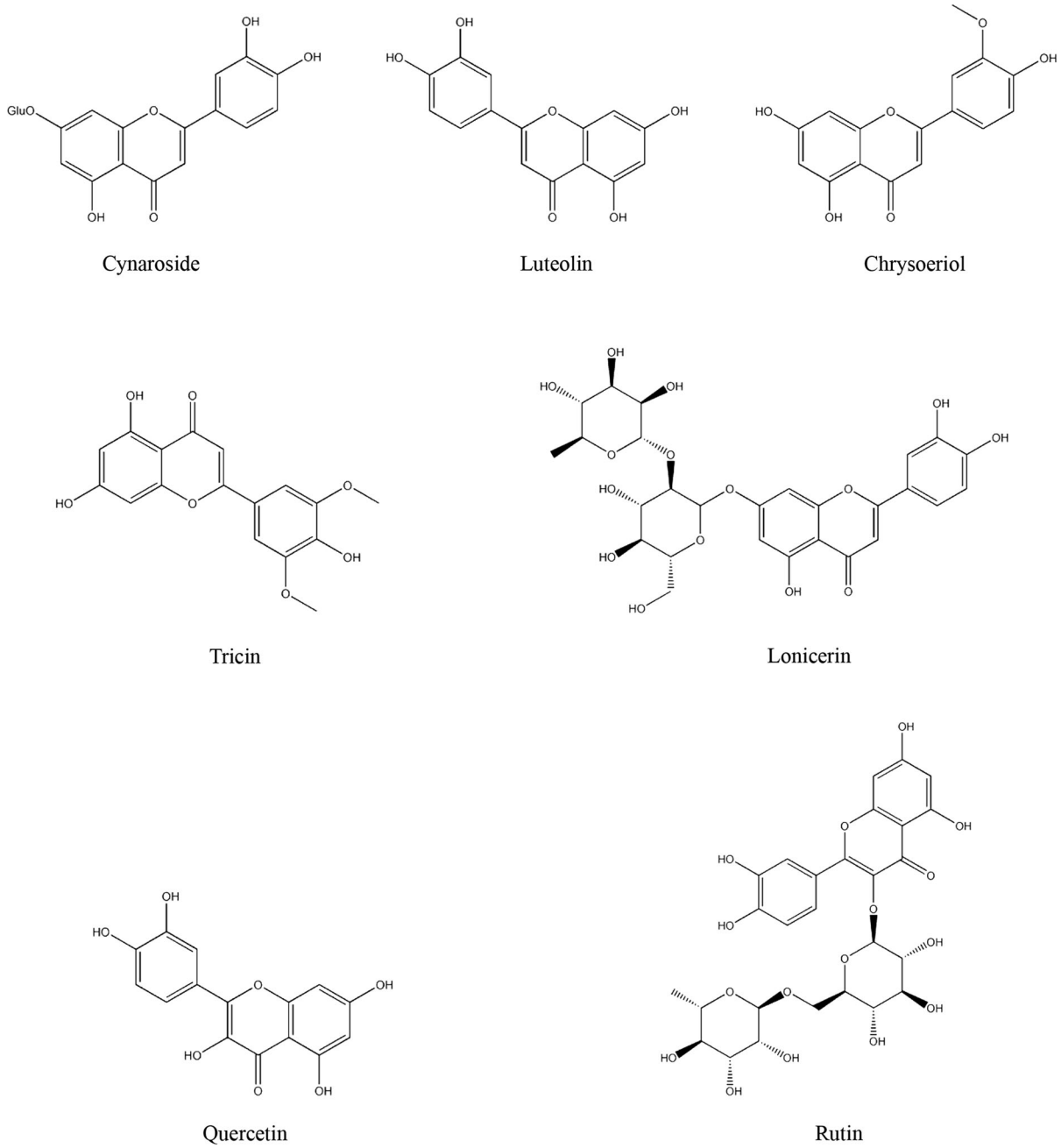


Fig. 3 The major flavonoids presenting in both JYH and SYH

CGA containing an *O*-hydroquinone moiety is the most abundant phenolic acid in JYH and SYH, and it has been used as a marker to evaluate chemical qualities of JYH and SYH according to 2015 Edition ChP (Chen et al. 2017; Li et al. 2015; Iwahashi et al. 1986). CGA is an ester of CA and quinic acid, and CA showed the strongest anti-inflammatory activity among **1–6**, **62** and **69** in vitro (50 μg mL^{-1}) (Song et al. 2015b). In addition, both CGA and CA can inhibit nitric oxide (NO) production, tumor necrosis

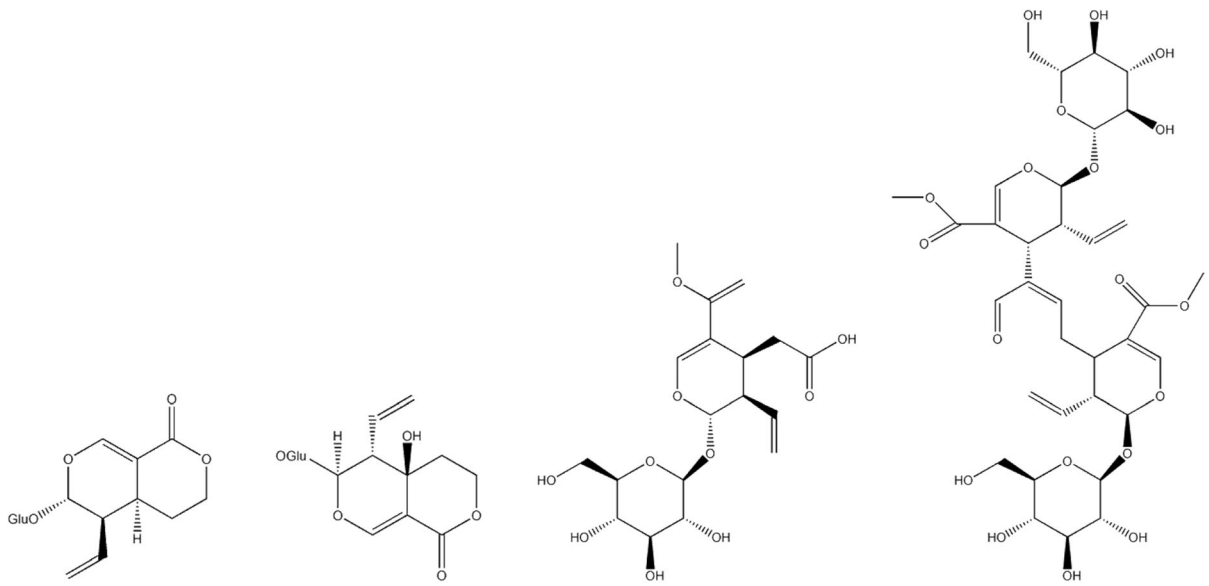
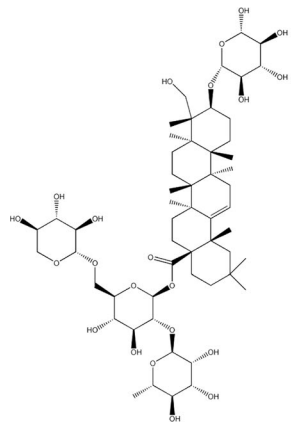


Fig. 4 The major iridoids presenting in both JYH and SYH

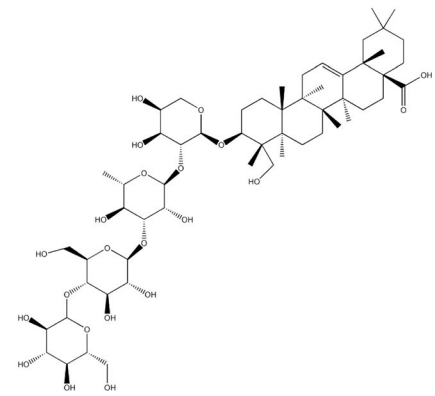
factor-α (TNF-α) and IL-6 secretion below 100 μg mL^{-1}, and exert effects on multiple targets, such as pro-inflammatory protein inducible nitric oxide synthase (iNOS), toll-like receptor 4, interleukin (IL)-1 receptor, matrix metalloproteinase-2 and 9 in vitro and in vivo, suggesting developing values (shown in Fig. 6) (Lee et al. 2012; Shi et al. 2013; Hou et al. 2017; Kim et al. 2014; Rubio et al. 2013). By reinforcing immune-resistance to bacteria and stimulating the activity of lysozym, CA affects the growth of some Gram-negative bacteria directly, such as *Pseudomonas fluorescens* (Ferrazzano et al. 2009).

Zhou investigated the pharmacokinetics and tissue distribution of CGA via oral administration. Employing noncompartment model, profile revealed CGA the low oral bioavailability (t_{max} = 0.58 ± 0.13 h, C_{max} = 1490 ± 0.16 μg L^{-1}), and tissue study showed that the highest level of CGA was in liver (Zhou et al. 2014). To study the bioavailability of CGA that extracted from JYH, Zhou gave 42 rats 400 mg kg^{-1} JYH 85% ethanol extractions (yielding an extraction with the content of 16.7% CGA) by intravenous (i.v), intramuscular (i.m) and intragastrical (i.g) administration. $t_{1/2}$ of i.v, i.m and i.g administration were 0.44, 0.50 and 0.38 h, and $AUC_{0\rightarrow\infty}$ were 6931.62, 6550.34 and 2591.87 μg h L^{-1}. The absolute bioavailability of CGA by i.g administration was only 37.39% (Ting et al. 2014). Chen developed a self-microemulsifying drug delivery system (SMEDDS) to improve the oral bioavailability of CGA. Compared with control group (CGA alone, t_{max} = 0.1 h, C_{max} = 82.6 μg mL^{-1}), CGA-SMEDDS group had a peak concentration of 47.6 μg mL^{-1} and the peak time was delayed to 2.4 h (Chen et al. 2017).

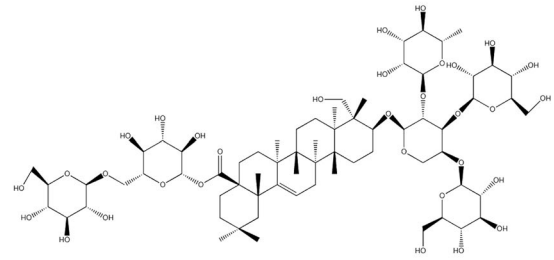
Phenolic acids are typically regarded as actives in a variety of bioassays as the above said, yet it should be stressed that orthoquinone substances readily display false-positive activities and act as interference in unrelated biological activities. The orthoquinone motif is characteristic of Pan Assay INterference compoundS, or PAINS (Baell 2016). CA and its derivatives, for instance, containing the recognizable PAINS motif (catechol), have a tendency to cause assay artifacts. Compounds with such functional group could undergo redox cycling, chelatesmetal, perturb membranes and appeared with signs of early structure–activity relationship (SAR) (Jasial et al. 2017; Baell and Holloway 2010), thus attracting attention of researchers and inevitably leading all efforts to be in vain.



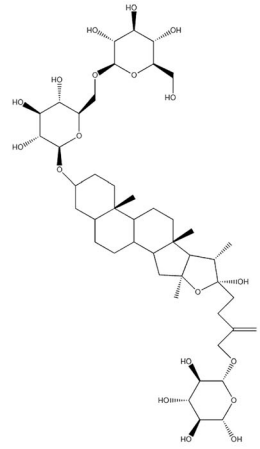
Macranthoidin A



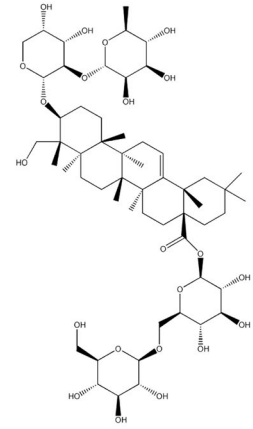
Macranthoside B



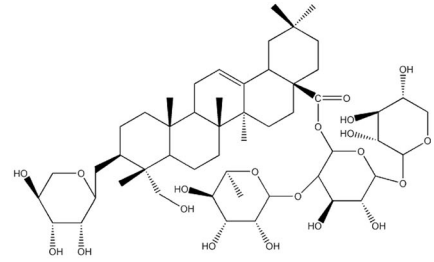
Macranthoidin B



Macranthoside A



Dipsacoside B



Loniceroside A

Fig. 5 The chemical structures of main saponins in SYH

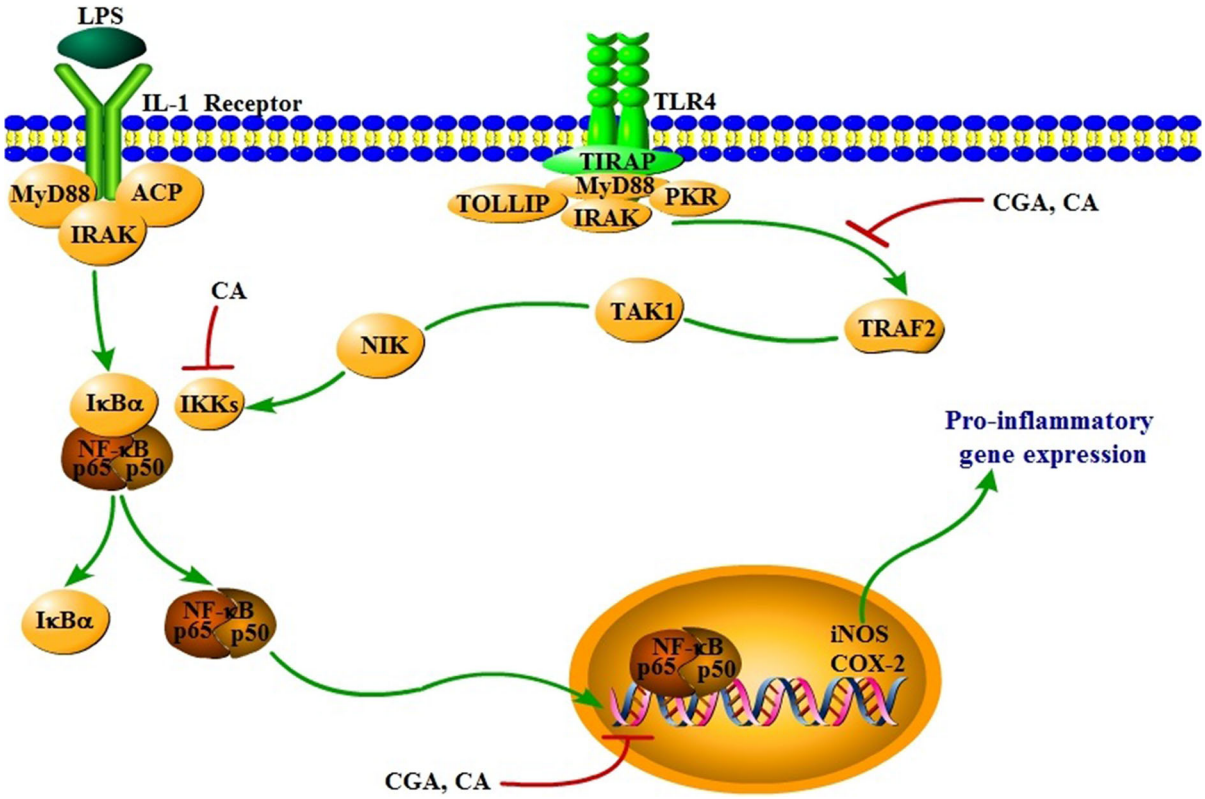


Fig. 6 Proposed molecular mechanisms of anti-inflammatory activities of CGA **(1)** and CA **(62)**. *LPS* lipopolysaccharide, *IL-1* interleukin, *MyD88* myeloid differentiation primary response gene 88, *ACP* acyl carrier protein, *IRAK* interleukin receptor associated kinase, *IκBα* I kappa B alpha, *NF-κB* nuclear factor κB, *TLR4* toll-like receptor 4, *TIRAP* toll-interleukin 1 receptor domain-containing adapter protein, *TOLLIP* toll interacting protein, *PKR* double-stranded RNA-dependent protein kinase, *CGA* chlorogenic acid, *CA* caffeic acid, *TRAF2* TNF receptor-associated factor 2, *TAK1* transforming growth factor activated kinase-1, *NIK* NF-κB inducing kinase, *IKKs* inhibitor of NF-κB kinases, *COX-2* cyclooxygenase-2, *iNOS* inducible nitric oxide synthase

Flavonoids

Flavonoids are a group of structurally diverse natural or synthetic compounds which include parent cyclic structures and their *O*- and *C*-glycosylated derivatives (Rauter et al. 2018). So far, 52 and 16 flavonoids have been found in JYH and SYH, 14 of which are identical. Researches on flavonoids in SYH should be further developed. In view of the current limited research, *L. confusa* has more flavonoids than the other three origins of SYH.

This class of compounds is mainly flavonols and flavones, and most of them are glycosides. Their health benefits are particularly associated with the prevention of chronic degenerative diseases such as cancer, diabete and cardiovascular disease (Scalbert et al. 2005; Ramassamy 2006). Luteolin **(89)** is a tetrahydroxyflavone in which the four hydroxy groups are located at positions 3′, 4′, 5 and 7. It has been reported to possess anti-angiogenic activity in human umbilical vein endothelial cells and human retinal microvascular endothelial cells (below 5 μM, in vitro), which contributed to the inhibition on the pathogenesis of retinopathy of prematurity and tumor growth (Eleni et al. 2004; Park et al. 2012b). Luteolin **(89)**, as well as cynaroside (**88**) a derived glycoside of luteolin that is substituted by a β-D-glucopyranosyl moiety at the position 7 via a glycosidic linkage of luteolin, is active against inflammation. Odontuya reported that the anti-inflammatory effect of luteolin and cynaroside was dependent on their molecular structures, that is to say the presence of *ortho-*

Table 5 Differences in content (mg/g) of major compounds isolated from JYH or SYH

Compound	Extraction	JYH	SYH				References
			L. macranthoides	*L. hypoglauca*	*L. confusa*	*L. fulvotomentosa*	
Phenolic acids							
1	Methanol	2.931 ± 0.010	5.657 ± 0.010				Yang et al. (2016)
Flavonoids							
88	70% methanol	0.472 ± 0.010	0.060 ± 0.010	0.009 ± 0.010	0.057 ± 0.010	0.173 ± 0.010	Zhang et al. (2015)
125	Methanol	0.951 ± 0.008	0.081 ± 0.003	tr	0.011 ± 0.008	nd	Xiong et al. (2005)
126	Methanol	0.093 ± 0.001	nd	0.029 ± 0.002	0.059 ± 0.001	nd	Xiong et al. (2005)
Iridoids							
143	70% methanol	0.242 ± 0.010	0.120 ± 0.010	nd	0.056 ± 0.010	0.245 ± 0.010	Li et al. (2003), Zhang et al. (2015)
Saponins							
265	70% methanol	nd	6.90 ± 0.020	4.13 ± 0.080	6.46 ± 0.140	3.78 ± 0.070	Zhang et al. (2015)
266	70% methanol	nd	51.81 ± 0.670	24.68 ± 0.240	54.68 ± 0.300	1.06 ± 0.020	Zhang et al. (2015)
267	Methanol	nd	1.79 ± 0.03	1.72 ± 0.02	2.04 ± 0.04	nr	Chai et al. (2005)
268	Methanol	nd	1.25 ± 0.03	2.23 ± 0.06	tr	nr	Chai et al. (2005)
269	70% methanol	nd	12.16 ± 0.130	19.28 ± 0.300	6.10 ± 0.120	40.96 ± 0.140	Zhang et al. (2015)

tr trace, *nd* not detect, *nr* no record

dihydroxy groups at the B ring and hydroxy substitution pattern at C-5 position of the A ring could significantly contribute to anti-inflammatory and antioxidant activities of flavones (Odontuya et al. 2010).

Iridoids

Iridoids are the main water-soluble compounds in JYH and SYH, mostly presenting as glycosides (Yang et al. 2016). So far, 92 and 8 iridoids have been isolated and identified from JYH and SYH. JYH and SYH contain similar iridoids (7 out of 8 SYH iridoids could be isolated from JYH). Compared to the other three SYH plant origins, *L. fulvotomentosa* contains relatively few iridoids and only sweroside **(143)** has been isolated. Iridoid glycosides in JYH include loganin **(142)**, loganic acid **(189)**, 8-epiloganic acid **(190)**, among others. Secoiridoids in JYH are sweroside **(143)**, secologanoside **(144)**, secoxyloganin **(148)**, secologanin **(150)**, among others, and they are the main iridoids in SYH. In addition, JYH and SYH also contain a dimer iridoid glycoside centauroside **(146)**, with structure linked by a C–C double bond.

Secoxyloganin (**148**) and dimethylsecologanoside (**200**, both at 100 μg mL^{-1}) displayed inhibitory activities (53.1% and 49.3%, respectively) against influenza A virus (H1N1), while the positive control oseltamivir carboxylate (100 μg mL^{-1}) showed 45.5% inhibitory rate (Kashiwada et al. 2013). Lonijaposides O, R, T and W (**221**, **224**, **226**, **229**) were also reported antiviral activities against H1N1 with half maximal inhibitory concentration (IC_{50}) values of 6.8–11.6 μM. The positive control, oseltamivir, gave an IC_{50} value of 1.3 μM (Yu et al. 2013). Centauroside (**146**) and (E)-aldosecologanin (**185**) exhibited much more potent NO inhibitory activities than the positive control minocycline in vitro (IC_{50} = 20.07 ± 0.37 μM), with IC_{50} values of 7.96 ± 0.47 and 12.60 ± 1.50 μM, respectively.

Table 6 The activities of some compounds isolated from JYH or SYH

Effect	Origins	Compounds	Model/targets	Positive control	Formulation/dosage	Result/mechanism/method	References
Anti-inflammatory activity	JYH	**1–6**, **62**, **69**	LPS-induced macrophage		In vitro 50 μg mL^{-1}	Inhibited NO production, TNF-α and IL-6 secretion	Song et al. (2015b)
		238	Croton oil-induced ear edema mouse Administered orally	Reference compounds prednisolone showed potent inhibition 57.9% inhibition at 10 mg kg^{-1} and aspirin weakly inhibited ear edema 15.0% inhibition at 100 mg kg^{-1}	In vivo 100 mg kg^{-1}	Inhibited ear edema 31%	Kwak et al. (2003)
	1	**281**	RAW264.7 macrophages	The presence of Indomethacin 10 μmol L^{-1} only produced a significant reduction of COX-2 mRNA expression	In vitro 10 and 100 μmol L^{-1}	Inhibited mRNA expression and COX-2 activity in a dose-dependent manner. Only high concentration 100 μmol L^{-1} reduced COX-1 expression	Guan et al. (2014a)
		282, **283**	LPS-activated RAW264.7 cells	Betamethasone, 30 μmol L^{-1}	In vitro 30 μmol L^{-1}	Inhibited expression of pro-inflammatory proteins iNOS and NO releasing	Mei et al. (2019)
Bacteriostatic activity	JYH and SYH	**1**, **4**	*P. aeruginosa*			The most correlated compounds against antibacterial activities assayed by canonical correlation analysis	Shi et al. (2016)
Antiviral activity	JYH	**1**, **62** and quinic acid	HepG2.2.15 cells cultured for 8 days in the presence or absence of **1**, **62** and quinic acid Duck hepatitis B virus DHBV-infected duckling model Administered orally	Lamivudine In vitro Exhibited an inhibition of HBsAg secretion at a IC_{50} value of 295 μM In vivo Inhibitory efficacy 50 mg kg^{-1} was lower than that of **1** and **62**	In vitro 0.14 to (1000) μg L^{-1} In vivo 100 mg kg^{-1}	In vitro **1** and **62** inhibited HBsAg secretion at an IC_{50} value of 242 μM and 13 μM, but showed little inhibition of HBeAg secretion at a dose up to (1000) μM In vivo **1** and **62** reduced the DHBV viremia significantly while DHBV viremia was slightly changed by quinic acid, indicating **1** and **62** having potent anti-HBV activities	Wang et al. (2009a)
	JYH	**1–4**, **6**	H1N1 virus	Ribavirin, 20 mg kg^{-1}		The order of antiviral intensities was ranked as followed, **4** ≈ **3** > **2** ≈ **1** ≈ **6**	Zhou et al. (2017)
	JYH	**148**, **200**	H1N1 virus	Oseltamivir carboxylate, 100 μg mL^{-1} 45.5% inhibition	In vitro 100 μg mL^{-1}	**148** and **200** had inhibitory activities against H1N1 replication inhibitory rates were 53.1% and 49.3%, respectively	Kashiwada et al. (2013)

Table 6 continued

Effect	Origins	Compounds	Model/targets	Positive control	Formulation/dosage	Result/mechanism/method	References
Anti-tumour activity	1	**267**	Tumour cell lines of different histogenetic origins four leukaemia types, HL-60, U-937, Jurkat and K-562. Two solid tumour-derive types, LoVo and Hep G2		In vitro 5, 10, 15 and 20 μmol L^{-1}	Inhibited cell growth of six cancer cell lines, especially human acute promyelocytic leukaemia HL-60 cells, with an IC_{50} value of 3.8 mmol. After 24 h and 48 h treatment, a hypodiploid cells assay and an annexin-V-FITC/PI double staining assay showed that there was a significant increase of apoptosis on HL-60 cells in a dose-dependent manner through caspase-mediated pathway, by activation of caspase-3	Guan et al. (2011)
	1	**267**	Human ovarian cancer A (2780) cells		In vitro 5, 10 and 20 μmol L^{-1}	Induced apoptosis and autophagy via reactive oxygen species ROS which could activate caspase-3 and caspase-9, cleave poly adenosinediphosphate- ribose polymerase, regulate adenylate-activated protein kinase, and inhibited mammalian target of rapamycin. Inhibits 70% colony formation at the concentration of 20 μmol L^{-1}	Shan et al. (2016)
	1	**267**	Human hepatoma HepG2 cells Female athymic BALB/cA nude mouse Intravenous injection	Cyclophosphamide, 25 mg kg^{-1} In vitro Had little inhibitory effect In vivo Tumors in mice treated with **267** and Cyclophosphamide resulted in 53.29% and 68.58% inhibition	In vitro 4.25, 7.08, 14.75, 23.04, 48.00 μmol L^{-1} In vivo 5 mg kg^{-1}	In vitro With concentration increasing, the inhibitory rates increased 2.58, 23.21, 55.89, 86.55 and 98.14%, with IC_{50} value of 10.10 ± 0.93 μM In vivo The volume and weight of xenograft tumors in mice were decreased remarkably $P < 0.05$	Wang et al. (2009b)

1—*L. macranthoides*

What's more, neither of them showed significant cytotoxicity at the concentration of 100 μM (Liu et al. 2015). In this literature, it also mentioned that secoiridoid glycosides had a more positive effect on α-glucosidase inhibition than other iridoid glycosides, while the presence of a methoxy group at C-7 or a double bond at C-6 or C-7 appeared to reduce the inhibition markedly.

Saponins

A large number of studies indicate that saponins contented in JYH are fewer than those in SYH (Li et al. 2003; Chai et al. 2005; Zhang et al. 2015; Yang et al. 2016). Saponins are the most compounds in SYH (Fig. 5), and most of them belong to the oleanane type or hederagenin type. Although most researches focus on *L. macranthoides*, macranthoidin A **(265)**, macranthoidin B **(266)** and dipsacoside B **(269)** which are the representative saponins in SYH, have been isolated from all four origins of SYH. It was relatively easy to distinguish *L. fulvotomentosa* from the other three SYH origins for *L. fulvotomentosa* having a relative low content of macranthoidin B **(266)** (Zhang et al. 2015; Chen et al. 2007; Zhou et al. 2014; Gao et al. 2012). Macranthoidin B **(266)** and dipsacoside B **(269)** have been used as markers to evaluate the chemical quality of SYH, whereas they are trace in JYH.

Studies showed that these saponins have anti-tumour and anti-inflammatory activities in vitro and in vivo (Kwak et al. 2003; Mei et al. 2019; Shan et al. 2016). In recent years, macranthoside B **(267)** has provoked mounting attention due to its anti-tumour activity both in vitro and in vivo with IC_{50} values in the range of 3.8–20 μM, and it could inhibit growth of various tumour cells through caspase-3 and caspase-9 pathways (shown in Fig. 7) (Guan et al. 2011; Shan et al. 2016; Wang et al. 2009b). Loniceroside C **(238)**,

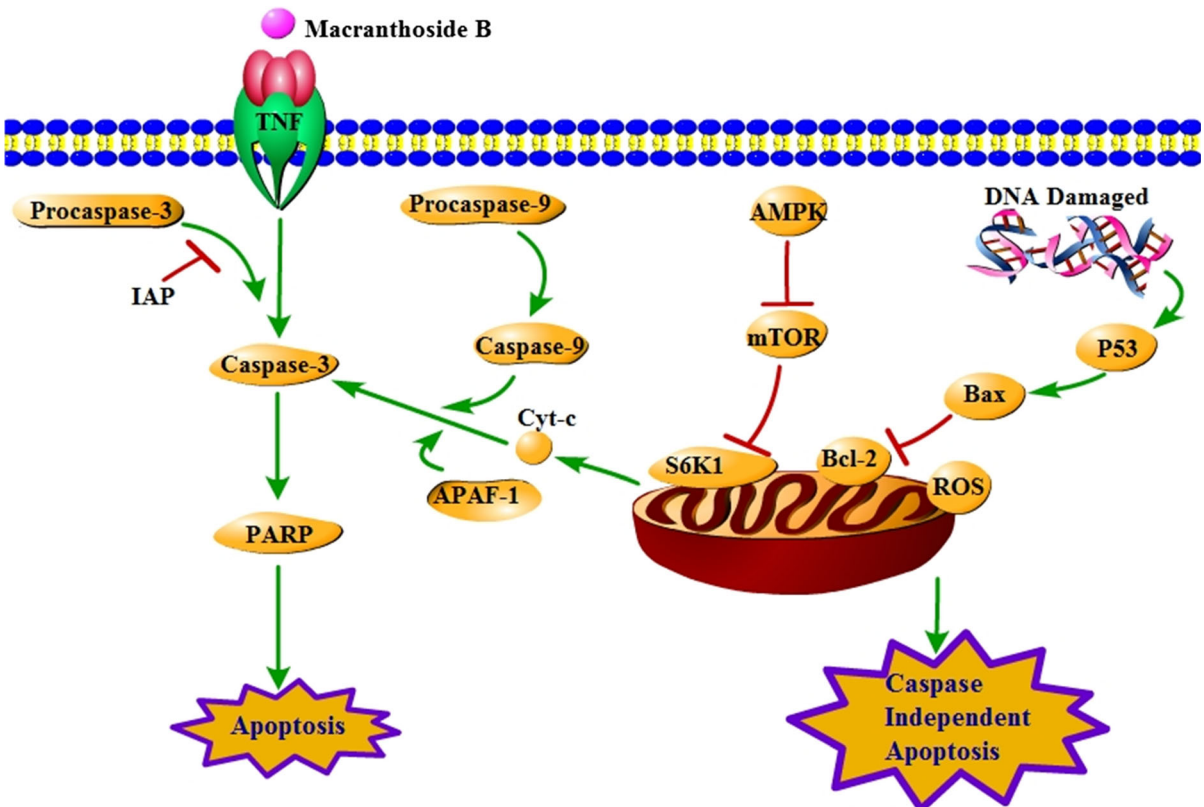


Fig. 7 Proposed molecular mechanisms of anti-tumour activitiy of macranthoside B **(267)**. *TNF* tumor necrosis factor, *IAP* immunosuppressive acidic protein, *PARP* poly adenosinediphosphate-ribose polymerase, *APAF-1* apoptotic protease activating factor-1, *Cyt-c* cytochrome c, *AMPK* adenosine 5′-monophosphate-activated protein kinase, *mTOR* mammalian target of rapamycin, *S6K1* p70 S6 kinase 1, *Bcl-2* B cell lymphoma-2, *Bax* B-cell lymphoma-2 associated X protein, *ROS* reactive oxygen species

macranthoside A **(268)**, dipsacoside B **(269)** and dipsacoside VI **(270)** have been reported anti-inflammatory activities both in vitro and in vivo (Kwak et al. 2003; Lee et al. 1995; Guan et al. 2014a; Mao et al. 1993), associating with many targets, such as prostaglandin E2 (PGE2), cyclooxygenase (COX)-1, COX-2, etc. In RAW264.7 macrophages, over-production of PGE2 was induced by lipopolysaccharide (LPS). Measuring COX activity and mRNA expression, the results showed that lonimacranthoide VI (**281**, 10 μmol L^{-1}) from *L. macranthoides* could inhibit mRNA expression and COX-2 activity in vitro, indicating lonimacranthoide VI **(281)** an important anti-inflammatory compound of SYH (Guan et al. 2014a). However, available evidence indicates that saponins have the potentiality to trigger cytotoxicity, and the sequence α-L-Rha*p*-(1 → 2)-α-L-Ara*p* in oleanolic acid or hederagenin is the characteristic of a more cytotoxic saponin (Park et al. 2001; Barthomeuf et al. 2002; Chwalek et al. 2006). This part will be discussed in Toxicology.

Essential oil

The aromas of JYH and SYH are unique and they both contain a large amount of essential oils which are edible natural perfume used in food, cigarettes and cosmetics (Wang et al. 2008). Essential oils of JYH and SYH are mainly composed of acids, aldehydes, alcohols, ketones and their esters, such as hexadecane **(291)**, nonadecane (**292**), hexadecanoic acid methyl ester (**294**). The content of acids in essential oils of JYH is relatively high, reaching 8.53% (Wu et al. 2009), while the content of linalool **(295)** in essential oils of SYH is the highest (Tong et al. 2005).

Others

Nucleosides, alkaloids, triterpenoids, etc. have also been isolated from JYH. Citric acid (**421**) has been isolated from SYH. In 2008, Li isolated a new compound with an unusual 1,2-dioxine skeleton, Shuangkangsu (**420**). It has prominent antiviral activity against influenza B virus and influenza A3 virus with treatment index (TI) greater than 32 ($P < 0.5$), and inhibits respiratory syncytial virus significantly with an IC_{50} value of 0.9 mg mL^{-1} (Li 2008).

Pharmacological activities

Modern pharmacological studies have revealed that JYH and SYH exhibit extensive range of biological activities. According to 2015 Edition ChP, they have same therapeutic actions. However, the reported studies indicated that some of their pharmacological effects are different, especially the discrepant intensities caused by the variation of bioactive compounds. This section describes the pharmacological activities of JYH and SYH, and presents their differences and similarities by reviewing their pharmacological studies (Table 7).

Anti-inflammatory activity

TNF-α, a major inflammatory mediator exerts systemic inflammatory properties such as fever and tissue damage, and possesses a broad spectrum of biologic activities on many different targets. NO has a significant role in homeostasis and host defense, and is tumoricidal and microbicidal along with its metabolites, NO_2^- and NO_3^-. However, over-production of NO becomes a key mediator of tissue damage (Nathan 1992; Pendino et al. 1993; Kroencke et al. 1991). JYH and SYH could inhibit TNF-α, nuclear factor (NF)-κB, IL-(1β, 6, 8) secretion and NO production significantly and enhance IL-10 expression below 0.4 mg kg^{-1} in vitro and in vivo, thereby showing anti-inflammatory activities (Kao et al. 2015; Li et al. 2016; Feng and Li 2008). However, reported pharmacological studies showed no significant difference in anti-inflammatory activity of JYH and SYH.

In trypsin-induced mast cell, Kang confirmed that water extraction of JYH (10, 100 and 1000 μg mL^{-1}) could inhibit trypsin-induced extracellular signal-regulated kinase (ERK) phosphorylation and did not affect the trypsin activity even at the concentration of 1000 μg mL^{-1}, indicating JYH inhibition of trypsin-induced mast cell activation through inhibiting ERK phosphorylation rather than trypsin activity in vitro (Kang et al. 2004). Li compared the inflammatory activities of water extractions of JYH and SYH with 1 μM Dexamethasone (DEX) as positive control. Both JYH (0.1532, 1.532, 15.32, 153.19, 306.38, 612.77 μg mL^{-1}) and *L. macranthoides* (0.1645, 1.645, 16.45, 164.54, 329.08, 658.16 μg mL^{-1}) exerted anti-inflammatory activity, but *L. macranthoides* showed a stronger inhibitory intensity of TNF-

Table 7 The modern pharmacological studies of JYH and SYH

Effect	Origins	Extracts	Model	Formulation/dosage	Result/method	Reference
Anti-inflammatory activity	JYH	Water	Trypsin-induced mast cell	In vitro 10, 100 and 1000 μg mL^{-1}	Inhibits TNF-α secretion in a dose-dependent manner and trypsin-induced ERK phosphorylation. At the concentration of 100 μg mL^{-1}, significantly inhibits TNF-α secretion. At the concentration of 1000 μg mL^{-1}, inhibits TNF-α secretion up to 71%	Kang et al. (2004)
			LPS-induced rat liver sepsis	In vitro 100 mg kg^{-1}	Inhibits the increase of NF-κBp65 and the degradation of I-κBα	Lee et al. (2001)
			Macrophage-like cell line (RAW 264.7 cells)	In vitro 2.0 mg mL^{-1}	Inhibits 66% NO production and 70% TNF-α secretion. Even at low concentration (0.0625 mg mL^{-1}), TNF-α secretion is also significantly inhibited ($P < 0.05$)	Park et al. (2005)
			LPS-induced acute lung inflammation mouse Administered orally	In vivo 0.4 mg kg^{-1}, 4 mg kg^{-1} and 40 mg kg^{-1}	Enhances the expression of IL-10 and decreases the NF-κB binding activities by increasing the nuclear Sp1 binding activity (the up-regulation of Sp1 activity is through incremental phosphorylation of ERK). Therefore, inhibites the expressions of TNF-α, IL-1β and IL-6, and the protein concentrations and nitrite/nitrate ratios in BALFs of mouse exposed to LPS are significantly suppressed	Kao et al. (2015)
	JYH and 1		Cigarette smoke extract-induced acute stomatitis KB cells	In vitro JYH: 0.1532, 1.532, 15.32, 153.19, 306.38, 612.77 μg mL^{-1} SYH: 0.1645, 1.645, 16.45, 164.54, 329.08, 658.16 μg mL^{-1}	Inhibit the expressions of TNF-α, IL-6 and IL-8, and improve low expression of IL-10 in a dose-dependent manner	Li et al. (2016)
	Total saponins of 2	Unknown	Ovalbumin-induced inflammation mouse	In vivo 200 mg kg^{-1}	Effectively reduce the over expressions of IL-6 and IL-17A, and significantly enhance the expressions of $CD4^+$ and $CD25^+$, and make T cell specific transcription factor Foxp3 regularity	Feng and Li (2008)

Table 7 continued

Effect	Origins	Extracts	Model	Formulation/dosage	Result/method	Reference
Bacteriostatic activity	JYH	Water		In vitro 40 mg mL^{-1}	Against *Bacillus cereus*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Escherichia coli*, and S*almonella anatum* (intensity: *E. coli* > *S. aureus* > *B. cereus* > *S. anatum* > *L. monocytogenes*) Gram-positive bacteria are generally more sensitive than Gram-negative bacteria to JYH	Shan et al. (2007)
				In vitro 10 mg mL^{-1}	Against oral pathogenic microorganisms	Bi et al. (2014)
	3, 4			In vitro 20 g kg^{-1}	Against *S. aureus*, *Typhoid bacillus* and *Dysentery bacillus.* The inhibitory effects of *L. confuse* are higher than those of *L. hypoglauca*	Li and Cui (1999)
	JYH and 1			In vivo 100 mg mL^{-1}	Prolong the survival time of *S. aureus*-infected mouse significantly ($P < 0.01$)	Lei et al. (2005)
Antiviral activity	JYH				Against human immunodeficiency virus, adenovirus, herpes simplex virus-1 (HSV-1), HSV-2 and H1N1	Zhou et al. (2017), Ou et al. (2015)
	SYH				Against NDV, PRV	Wang et al. (2011a), Wang et al. (2011b)
Liver protective activity	JYH		AP-induced liver injury mouse	In vivo 350 mg kg^{-1}	Inhibits the increase of AP-induced alanine and aspartate transaminases (ALT/AST) enzymatic activities, as well as total bilirubin (TB) amount	Jiang et al. (2014)
			Dimethylnitrosamine (DMN)-induced acute liver injury wistar rats	In vivo 200 mg mL^{-1}	Liver fibrosis is significantly reduced	Sun et al. (2010)
	2		Ethylphthalide aminophenol (AM)-induced hepatotoxicity mouse	In vivo 100 mg kg^{-1}	Enhances the detoxification of liver to AM and alleviates mouse liver injury	Shi and Liu (1995)
	JYH and SYH		CCl_4-induced liver injury mouse	In vivo 200 mg kg^{-1}	Decrease serum glutamic-pyruvic transaminase, liver triglyceride and MDA levels significantly ($P < 0.05$)	Tang et al. (2016)

Table 7 continued

Effect	Origins	Extracts	Model	Formulation/dosage	Result/method	Reference
Antioxidative activity	JYH		High pressure steam-scalded mouse	In vivo 1 g mL^{-1}	Polymorphonuclear (PMN) lysyme release rate reduces significantly	Luo et al. (1994)
	SYH			In vitro 250 μg mL^{-1}	Scavenges $O2^{-}\cdot$ and ·OH effectively.	Wu et al. (2015b), Xu et al. (2014)
Hypoglycemic activity	JYH polysaccharides		STZ-inducd diabetic rats	In vivo 800 mg kg^{-1}	The contents of liver and skeletal muscle glycogen and the concentrations of hepatic pyruvate kinase and hexokinase increases, together with significant declining of total cholesterol, totaltriglyceride, low-density and very-low-density lipoprotein-cholesterin and significant rising of high-density lipoprotein-cholesterin. Inhibit the increasing sugar, insulin levels and the food and water intake.	Wang et al. (2017a), Zhao et al. (2018)
	SYH polysaccharide		STZ-induced diabetic rats Administered orally	In vivo 800 mg kg^{-1}		
Anti-tumour activity	JYH polyphenolic		Human hepatoma HepG2 cell line	In vitro 10 mg mL^{-1}	Decreases the expressions of cyclin dependent kinase 1, cyclin B1, pro-caspases-3, pro-caspases-9 and poly adenosine diphosphate ribose polymerase. The phosphorylation of ERK ½, c-Jun N-terminal kinase (JNK), and MAPKs are increased, whereas Akt is dephosphorylated.	Park et al. (2012a)

1—*L. macranthoides*, 2—*L. fulvotomentosa*, 3—*L. hypoglauca*, 4—*L. confusa*

α and IL-6 secretion than JYH did ($P < 0.05$) (Li et al. 2016). However, this study lacked content consistency, which further compromised the accuracy of results.

In another study, LPS-induced acute lung inflammation mice were administered with different concentrations of JYH water extraction (0.4 mg kg^{-1}, 4 mg kg^{-1} and 40 mg kg^{-1}) orally for 24 h. Then, the cytokine concentrations (TNF-α, IL-1β, IL-10 and IL-6) in the bronchoalveolar lavage fluids (BALF) were measured by enzyme-linked immunosorbent assay (ELISA). The results showed that JYH had protective activity against LPS-induced lung inflammatory cytokine releasing in vivo (Kao et al. 2015). All these studies suggested that both JYH and SYH could inhibit inflammatory reaction, but few studies compared them systematically and then told their similarities or differences.

The studies regarding anti-inflammatory activity of JYH in preparations are abundant, while studies of that on SYH are limited. Cheng studied anti-inflammatory activities of a traditional herbal formula which was consisted of Rosae Multiflorae Fructus and JYH (50:30, V/V) in LPS-stimulated RAW 264.7 macrophages. Ethanol extraction of this formula (containing JYH 5 mg mL^{-1}) dose-dependently inhibited NO, IL-6, TNF-α productions and cellular iNOS protein, COX-2 expressions by the NF-κb and mitogen-activated protein kinases (MAPKs) signalling pathways in vitro (Cheng et al. 2014). Gingyo-san (1 mg kg^{-1}, water extraction), a traditional Chinese medicinal formula which includes JYH could reduce acute lung inflammation in LPS-induced lung inflammation mice compared with the control mice ($P < 0.05$) by reducing the infiltration of activated polymorphonuclear neutrophils in the airways, decreasing pulmonary edema, reducing nitrosative stress, and improving lung morphology in vivo through administered it orally. The mechanism of anti-inflammatory activity of Gingyo-san was attenuating expressions of TNF-α, IL-1, IL-6, and activating NF-κB in BALF and lung tissue. Particularly, Gingyo-san also enhanced the expression of IL-10 (Yeh et al. 2007).

Bacteriostatic activity

JYH and SYH have similar antibacterial spectrum, and their water extractions could inhibit *Escherichia coli*, *Shigellosis, Bordetella pertussis*, *Sarcina lutea*, *Bacillus subtitles*, *Mycobacterium tuberculosis*, *Staphylococcus*, *Pseudomonas aeruginosa*, *Streptococcus*, *Diplococcus pneumoniae*, etc. effectively (40 g kg^{-1}) (Lei et al. 2005). However, the antibacterial intensity of JYH was stronger than that of SYH (Shi et al. 2016; Lei et al. 2005), and there was a highly positive relationship ($R^2 = 0.73–0.93$) between antibacterial activity and the content of phenolic acids (Shan et al. 2007). What's more, phenolic acids, reaching the highest concentration in the tissues of digestive tract, particularly the oral mucosa, have strong effect to prevent oral diseases (Petti and Scully 2009). Thereby, regular consumption of JYH and SYH may help prevent oral diseases.

Using a bacterial model (*P. aeruginosa*), the relationship of antibacterial activities between JYH and SYH (70% ethanol extractions) was evaluated. The antibacterial activities of JYH and SYH should be divided into two clusters by multivariate statistical analysis, and the results supported the disaggregation of JYH and SYH by the Pharmacopoeia Committee. Meanwhile, the inhibition effects of JYH (100 mg mL^{-1}) on *P. aeruginosa* were similar regardless of geographical origins. In contrast, the inhibition effects of SYH (100 mg mL^{-1}) on *P. aeruginosa* were not stable, indicating JYH a more stable quality and activity (Shi et al. 2016).

Antiviral activity

JYH was the most popular herb used in treatments of severe acute respiratory syndromes (SARS) and influenza A in 2003 and 2009 (Yang et al. 2017a). Phenolic acids were regarded as main antiviral compounds of JYH and SYH. According to Wang's study, 60% ethanol extractions of both JYH (1 mg mL^{-1}) and SYH (1 mg mL^{-1}) could inhibit the infection of Newcastle Disease Virus (NDV), but there was no significant difference between them ($P > 0.05$). Flavonoid extractions (extracted by 70% ethanol) of JYH (1 mg mL^{-1}) and SYH (1 mg mL^{-1}) had significant antiviral activities against pseudorabies virus (PRV) in vitro, between which SYH had stronger inhibitory effect on PRV (Wang et al. 2011a; Wang et al. 2011b).

Liver protective activity

Acetaminophen (AP)-induced hepatotoxicity was the most common acute liver injury in both the United States and the United Kingdom (Lee 2004; Zhou et al. 2017). To date, JYH, *L. macranthoides* and *L. fulvotomentosa* have already been confirmed liver protective activities through various in vitro and in vivo trials (Jiang et al. 2014; Sun et al. 2010; Shi and Liu 1995), and there was no significant difference in liver protective activities between them (Tang et al. 2016).

On one study, by TdT-mediated biotin-dUTP nick-end labeling (TUNEL) assay, Jiang found that AP increased the number of apoptotic hepatocytes in mice ($P < 0.001$), while JYH (350 mg kg^{-1}, water extraction, administered orally) obviously decreased this tendency ($P < 0.001$). *N*-Acetylcysteine (NAC, 600 mg/kg as positive control) chould also obviously ameliorate AP-induced liver injury. Detected by cell viability (CV) assay, AP-induced cytotoxicity in human normal liver L-02 cells could be reversed by CGA **(1)**, isochlorogenic acid A–C **(3–5)** and CA **(62)** of JYH, while flavonoids [cynaroside **(88)**, luteolin **(89)**, hyperoside **(130)**], iridoids (swertiamarin) and essential oils [linalool **(295)** and geraniol **(325)**] had no protective activities against AP-induced hepatotoxicity. Thus, JYH could prevent AP-induced liver injury in vivo by inhibiting apoptosis, and phenolic acids may be the main hepato-protective active compounds in JYH (Jiang et al. 2014). What's more, phenolic acids alleviating AP-induced hepatotoxicity could also prevent liver injury induced by various chemical compounds such as carbon tetrachloride and thioacetamide (Wu et al. 2007; Mancini-Filho et al. 2009). On the other study, SYH saponins were reported to exert protective activities on liver injury in vitro and in vivo caused by acetaminophen, Cd, and CCl_4 distinctly (Ferrazzano et al. 2009; Ji et al. 2013). In D-aminogalactose and CCl_4-induced liver injury rats, water extractions of both *L. macranthoides* and *L. fulvotomentosa* (150 mg kg^{-1}) showed liver protective activities (Shi et al. 1999). These results revealed that JYH and SYH had potential to be developed as a new drug against liver injury. However, these studies lacked positive control and further studies require more in-depth, including exploring the related pathways and searching for the targets.

Antioxidative activity

Phenolic acids are well-known antioxidants used as nutritional supplements to enhance the antioxidative capacity of body (Jiang et al. 2014). CGA **(1)** and CA **(62)** are powerful antioxidants in vitro and in vivo (Wang et al. 2009a). Flavonoids, especially cynaroside **(88)** which can remove free radicals of ultra oxygen ions in body could increase immunity and delay senescence (Yang et al. 2017a). Antioxidative activity of JYH presented a significant positive correlation with the content of CGA **(1)**, cynaroside **(88)**, rutin **(125)** and hyperoside **(130)** (Kong et al. 2017). Studies on antioxidative activity of SYH also focus on its phenolic acids and flavonoids (Xu et al. 2014). So far, various pharmacological studies have confirmed potent antioxidative activities of JYH and SYH in vitro and in vivo (Chen et al. 2013; Shang et al. 2011; Guo et al. 2014; Xu et al. 2014). What's more, SYH may have higher antioxidative intensity than that of JYH according to the current research (Xiao et al. 2019). 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic) acid (ABTS+) scavenging assay is the most frequently used antioxidative activity assay for it could measure antioxidative activity in a rapidly and directly simple manner (Lee et al. 2011).

JYH

Seo measured antioxidative activities of 70% methanol extractions of JYH (25, 50, 100, 250, 500, and 1000 mg L^{-1}) by ABTS+ and reducing power (RP) assays, with butylated hydroxytoluene (BHT, 25, 50, 100, 250, 500, and 1000 mg L^{-1}) as a positive control. The ABTS+ assay suggested JYH a significantly stronger antioxidative activity than BHT in vitro ($P < 0.05$) (Seo et al. 2012). Injectable SHL has been demonstrated antioxidative activity. In LPS-induced acute lung injury mouse, superoxide dismutase (SOD) and catalase (CAT) activities were markedly decreased, while malondialdehyde (MDA) was over-production. In contrast, injectable SHL (5 and 10 mL kg^{-1}) could decrease MDA content and the over-production of pro-inflammatory cytokines (TNF-α IL-1β, and IL-6) in vivo. What's more, 10 mL kg^{-1} SHL increased the SOD and CAT activities ($P < 0.05$). Histological studies demonstrated that SHL attenuated LPS-induced interstitial edema,

hemorrhage, and the infiltration of neutrophils into lung tissue (Fang et al. 2015).

SYH

Employing pyrogallol autoxidation and Fenton assays, Xu determined the free radicals scavenging ability of SYH flavonoids (extracted by 70% ethanol) in vitro, and measured the protective activity of SYH flavonoids on hydrogen peroxide-induced (H_2O_2-induced) oxidative injury endothelial cells and cardiomyocytes by methyl thiazolyl tetrazolium assay. The scavenging rates of superoxide anion free radical ($O_2^-\cdot$) and hydroxy free radical (·OH) were 42.40% and 64.99% respectively when the concentration of SYH flavonoids was 250 μg mL^{-1}. With SYH flavonoids pretreating, the survival rates of H_2O_2-induced oxidative injury endothelial cells and cardiomyocytes were upgraded to 60.45% and 69.98% (Xu et al. 2014), showing high antioxidative activities in vitro, similar conclusion with (Wu et al. 2015b; Xiao et al. 2019).

Using different solvents, the antioxidative activities of SYH may be different. Hu used in vitro antioxidative assays, ABTS+ and $O_2^-\cdot$ assays, as well as FRAP assay being selected to obtain complementary results, to evaluate different antioxidative activities of *L. macranthoides* (100 g L^{-1}) extracted by different solvents. The results showed n-butanol fraction had the highest ABTS+ and $O_2^-\cdot$ scavenging activities among water extraction, petroleum ether, ethyl acetate and n-butanol fractions (Hu et al. 2016).

The above studies show that both JYH and SYH possess potent antioxidative activities, suggesting them potential natural antioxidants in scavenging biologically relevant radicals. However, further researches should focus on evaluating their antioxidative activities in vivo and elucidating the antioxidant mechanism. Moreover, the differences of their antioxidative intensities are also worthy of further study.

Hypoglycemic activity

Diabetes mellitus (DM) a chronic metabolic disorder has become one of the world's most serious health concerns. Clinically, there are four types of DM, and type 2 diabetes mellitus (T2DM) is the most common form that causes many severe secondary complications, such as atherosclerosis, renal dysfunction and failure, cardiac abnormalities and ocular disorders (Rengasamy et al. 2013; Wang et al. 2015; Guo et al. 2015). Shin's study showed that CGA **(1)** (10 and 20 mg kg^{-1}, intraperitoneal injection) effectively preserved the expression of tight junction protein and attenuated STZ-induced diabetic retinopathy in mice (Shin et al. 2013). Nowadays, JYH has already been an ingredient of hypoglycemic CPMs for T2DM, and SYH has also been mentioned to be a potential therapy for T2DM.

In streptozocin (STZ)-inducd diabetic rats, the food and water intake and the levels of sugar and insulin were drastically decreased after orally administrating with water extraction of JYH or SYH (all 800 mg kg^{-1}). What's more, the contents of liver and skeletal muscle glycogen and the concentrations of hepatic pyruvate kinase and hexokinase increased, together with significant declining of total cholesterol, totaltriglyceride, low-density and very-low-density lipoprotein-cholesterin and significant rising of high-density lipoprotein-cholesterin, indicating JYH and SYH notable hypoglycemic activities in vivo (Wang et al. 2017a; Zhao et al. 2018).

Present studies showed that JYH and SYH exerted similar hypoglycemic activities, inspiringly, future researches asking more exploring of their differences and bringing into positive control.

Anti-tumour activity

JYH and SYH have already been confirmed anti-tumour activties on human hepatoma HepG2 cell, HL-60, U-937, Jurkat, ovarian cancer A2780, K-562 in vitro and in vivo (Park et al. 2012a; Guan et al. 2011; Shan et al. 2016). CA **(62)** and its derivatives could suppress tumor angiogenesis and retard tumor growth (Jung et al. 2007). Among them, CGA **(1)**, a well-known anti-tumour agent could up-regulate cellular antioxidant enzymes and suppress the ROS-mediated activation of NF-κB, activator protein-1, and MAPK (Feng et al. 2005). By inhibiting Akt and activating MAPKs, JYH polyphenolic extraction (10 mg mL^{-1}, extracted by 70% methanol) could inhibit proliferation of human hepatoma HepG2 cell line in vitro in a dose-dependent manner (Park et al. 2012a). In recent years, macranthoside B **(267)**, a hederagenin saponin in SYH showed great potential to be an anti-tumour agent for its capability of blocking cell proliferation and inducing cell death in several types of cancer cells through the caspase-mediated

pathways, such as caspase-3 and caspase-9 in vitro and in vivo (Shan et al. 2016; Guan et al. 2011; Wang et al. 2009b). Employing cell proliferation and xenograft tumor growth assays, Wang confirmed the anti-tumour activity of macranthoside B **(267)** both in vitro and in female athymic BALB/cA nude mouse, with IC_{50} value of 10.10 ± 0.93 μM.

Other activities

In addition to the pharmacological activities described above, JYH and SYH displayed other activities. Water extraction of JYH (100, 200 mg kg^{-1}, orally administered) could inhibit the increasing retinal vessels in both outer and inner plexiform layers in STZ-induced diabetic mice. Furthermore, it could reduce the increasing cell proliferation and tube formation induced by vascular endothelial growth factor (VEGF) in FR/6A cells with no cytotoxicity, showing inhibition property of JYH against VEGF-induced retinal angiogenesis in vitro (Zhou et al. 2016). Conversely, anti-angiogenic activity of SYH needed to be explored further. Xanthine oxidase (XO) is an enzyme related to hyperuricaemia. Employing enzymatic assay, Peng evaluated the XO inhibition activity of *L. macranthoides* water extraction in vitro. *L. macranthoides* extraction showed inhibition activity on XO with an IC_{50} value of 58.2 μg mL^{-1}. Isochlorogenic acid A–C **(3–5)** with dicaffeoyl groups exhibited effective XO inhibition with IC_{50} values of 189.6 ± 7.9, 96.2 ± 3.1 and 75.3 ± 2.6 μM, while compounds **(1**, **2**, **6)** with monocaffeoyl group showed weak XO inhibitory activities (10–15% inhibition at the concentration of 200 μM) (Peng et al. 2016).

Clinical use

Clinical indications of JYH and SYH are mainly related to inflammation, bacterial and virus infection. There are numerous clinical trials on JYH products and most of them focus on SHL. On the contrary, clinical studies on SYH remain rare.

Significant therapeutic effects on oral ulcer were taken by a standard double therapy with Ranitidine (0.15 g × 4/day) and Vitamins (20 mg × 3/day Vitamin B, 200 mg × 3/day Vitamin C) (RcV) or SHL Oral Liquid (20 mL × 3/day, equivalent to JYH crude drug 7.5 g/day) (RcS) (120 cases). Patients with RcS treatment showed to achieve higher rates of effectiveness ($P < 0.05$) than those with RcV. Immunoglobulin G and secretory immunoglobulin A levels of patients treated with RcS were better than those treated with RcV, promoting a healing of ulcer and improving the clinical symptoms of patients (Ying et al. 2019). The effect of JYH decoction combined with penicillin on the treatment of syphilis was assessed. In this study, a total of 92 syphilis patients were divided into two groups to treat with either penicillin $injection_{i.m}$ (2,400,000 U kg^{-1} d^{-1}, 1 times/week) or a combination of JYH decoction (30 g/day) and penicillin injection (PcJ) for 3 weeks. After the 3 months of treatment, the Th1/Th2 levels of PcJ group were significantly improved and IL-2, IL-8 and IL-10 were significantly decreased. These changes were statistically significant in comparison with the penicillin group (Zhao and Li 2018). Gao took SHL Oral Liquid (for children. 1–3 years old, 10 mL, tid; > 3–7 years old, 20 mL) combined with Recombinant Human Interferon α-2b injection (RHi, 100,000 U kg^{-1} d^{-1}) to treat children viral pneumonia (7 days of treatment, 55 cases). In comparison to using RHi alone, a combination with SHL Oral Liquid possessed higher effective rates, and antipyretic time as well as cough disappearance time was significantly shortened. What's more, the adverse reaction rates of them two showed no significant differences ($P > 0.05$) (Gao 2018). Wu took Fusidic Acid Cream (2 mm) as the control group and JYH decoction (30 g) combined with Fusidic Acid Cream (2 mm) as experimental group to analyze the clinical efficacy of JYH decoction in the treatment of targeted drugs-induced rash (80 cases). After treatment, the effective rates of experimental group (95.00%) were higher than those of control group (77.50%) ($P < 0.05$), and no statistical differences of adverse reaction rates were found between the two groups ($P > 0.05$) (Wu et al. 2017).

The above results showed JYH a high clinical application value. It could relieve the clinical symptoms effectively, and improve the quality of life. However, are these satisfactory clinical traits a placebo effect? Further study involving placebo group might help in the identification of work effort for JYH.

Quality control

Quality control of herbs is essential to ensure their efficiency and safety. According to 2015 Edition ChP, the content of CGA **(1)** and cynaroside **(88)** in JYH must be no less than 1.5% and 0.05%, and the content of CGA **(1)** and the total amount of macranthoidin B **(266)** and dipsacoside B **(269)** in SYH must be no less than 2.0% and 5.0% on the basis of high performance liquid chromatography (HPLC) calibration Standard Operating Procedure. However, current studies suggested that habitats, harvest time, extract methods may bring about differences in quality of herbs to some extent (Table 8). According to Table 8, GCD has a stable quality, and high-yield harvest phases of JYH should be S3-S5, just before the beginning of summer. Meanwhile, tetraploid JYH is an excellent breed for agricultural cultivation with high yields, stress tolerance and good quality. In daily storage of JYH and SYH, environment should keep cool due to some of their chemical compounds are thermosensitive (Lei et al. 2006; Wang et al. 2011c; Ji et al. 1990).

Traditionally, herbs are identified by morphological characteristics which primarily depend on human expertise. In some case, it is extremely difficult to definitively identify plant origins. With the development of chemical analysis, measuring an herb or CPMs rapidly and multi-content has become a consensus. Previous studies have provided JYH numerous reliable quality control methods. Yang used near infrared (NIR) spectroscopy technique combined with synergy interval partial least squares and genetic

Table 8 Factors influencing quality of JYH and SYH

Factors	JYH	SYH	Likely reasons	References
Habitats	GCD has a stable quality		May relate to the sunshine	Li et al. (2013), Chen et al. (2007), Yang et al. (2017a)
Ploidy	Tetraploid JYH has higher polyphenol contents, biomass yields, stronger resistance to drought and higher antioxidant activities than those in diploid JYH		Increases in gene dosage follow the plant genome duplications in nucleus. This process may not only bring about significant changes in morphology and physiology, but also increase the cell size and the content of secondary metabolites because of whole genome duplications. Herbs are especially significant, with growth rates enhancing and genetic quality improving	Lavania (2007), Sun et al. (2011), Van Laere et al. (2010), Kaensaksiri et al. (2011), Lavania et al. (2012), Kong et al. (2017), Gao et al. (2017), Li et al. (2011), Li et al. (1996), Li et al. (2009), Xiong et al. (2006)
Harvest time	The content of essential oils reaches the highest at S5, while the content of flavonoids reaches the highest at S3, and CGA is at S3 and S4			Yang et al. (2017b), Kong et al. (2017)
Extraction methods	Extraction yields of phenolic acids in JYH are associated with ethanol concentration	Hydrodistillation is the best choice to extract pure volatile fraction Ethyl acetate fraction exhibited the highest content of total phenolic acids and total flavonoids		Duan et al. (2018), Hu et al. (2016), Wu et al. (2015a)

algorithm to monitor extraction process of JYH. This method reliably monitored changes in the content of online extract process (Yang et al. 2017b). NIR spectra could also reflect the differences between batches. Li built an NIR fingerprint method, and proposed to use it in consistency check between batches, beneficial to industrial production (Li et al. 2013). Nevertheless, studies of quality control in SYH are limited, and most of them focus on distinguishing SYH from JYH, lacking researches on SYH exclusively.

JYH and SYH could be distinguished by normal light microscopy combined fluorescence microscopy. Under normal light microscopy, JYH and three origins of SYH (except *L. confusa*) could be distinguished by their traits of glandular hairs. By means of fluorescence microscopy, *L. confusa* was further identified with its transverse section partially distributing fluorescence materials (Chu et al. 2011). Through ultra HPLC with triple quadrupole mass spectrometry technology, cynaroside **(88)**, sweroside **(143)**, macranthoidin A **(265)**, macranthoidin B **(266)** and dipsacoside B **(269)** have been quantified as internal standard substances to check SYH adulterated in JYH preparations. The results showed that JYH could be easily distinguished from SYH by the total amount of saponins (0.067 mg g^{-1} for JYH and $>$ 45.8 mg g^{-1} for SYH).

Han used DNA barcoding, a molecular diagnostic technology identifying species by a short genomic sequence (Hebert et al. 2003), to investigate the varieties and proportions of adulterant species. The results indicated that ITS2 barcodes could be used to identify adulterants and JYH was one of the most adulterant species. Notably, given that some samples were heavily processed and there was no DNA barcoding in artificial adulterant sample, DNA barcoding technology was not sufficient to identify any given samples. In other words, DNA barcoding technology could be used to establish the authenticity of herbs or CPMs, but could not be used to evaluate the quality of herbs or CPMs (Han et al. 2016). Employing the modified cetyl trimethyl ammonium bromide method, genomic DNA was isolated from Fu Fang Yu Xing Cao Tablet, Lin Yang Gan Mao Tablet and Yin Qiao Jie Du Tablet (names of CPMs), which all contained JYH. Jiang used sequence and phylogenetic analyses to detect the species in prescriptions and the results showed that the above three CPMs were actually adulterated with SYH. Jiang's method was reproducibility and had characteristic of non-reliance on morphology, so it could be used in authenticating preparations so as to evaluate their quality (Jiang et al. 2013).

Nowadays, SYH adulterated in JYH is common. According to Zhang's study, eighteen of twenty one JYH preparations were adulterated with SYH in proportions of 11.3–100% (Zhang et al. 2015). Gao checked twenty extractions and 47 CPMs. The results showed that only 12 extractions and 33 CPMs were authentic. What's more, Gao's study revealed that some CPMs containing SYH were actually adulterated with high commercial value JYH, which indicated that the manufacturers may not distinguish JYH and SYH, giving a risk to a loss of revenue (Gao et al. 2017).

Above all, future research should value SYH in order to identify JYH and SYH better both in crude materials or CPMs.

Toxicology

To date, the toxicity studies on JYH are seldom reported, while those on SYH are relatively more. Studies on the toxicology of JYH and SYH are mainly focused on saponins. However, neither JYH nor SYH water extractions have significant toxicity on breathing, blood pressure or urine output (the half lethal dose (LD_{50}) $>$ 110 g kg^{-1}), far higher than their biologically active dose (Jiang et al. 2015; Thanabhorn et al. 2006). According to 2015 Edition ChP, the clinical administrations of JYH or SYH in an adult are suggested to be 6–15 g daily, indicating them low-toxicity herbs.

Wang researched hemolysis of macranthoidin B **(266)** and dipsacoside B **(269)** in vitro and in vivo. By observing hemolysis of them in rabbit red blood cells at the concentration of 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 mg L^{-1}, no hemolysis occured compared to the control group ($P > 0.05$). In vivo, macranthoidin B **(266)** (0.110 and 0.055 mg g^{-1}) and dipsacoside B **(269)** (0.020 and 0.010 mg g^{-1}) did not cause hemolysis (continuous tail vein administration for 7 days) (Wang et al. 2016). In another study, loniceroside A **(236)**, loniceroside B **(237)** (the major saponins in JYH), macranthoidin A **(265)**, dipsacoside B **(269)** and dipsacoside VI **(270)** (the major saponins in SYH) all did not cause hemolysis at the concentration of 1.0 mg mL^{-1} in vitro. The hemolysis rate of

macranthoidin A **(265)** rose with its concentration increasing. No hemolysis occurred when the concentration of macranthoidin A **(265)** was 0.6 mg mL^{-1}, and the hemolysis rate was 50.4% when the concentration of macranthoidin A **(265)** reached 1.0 mg mL^{-1}. When comes to the hemolysis of JYH compounds, the strength decreased as the following order, saponins, phenolic acids, iridoids. When the concentrations of iridoids were 0.1–1.2 mg mL^{-1} or phenolic acids was less than 1.0 mg mL^{-1}, no hemolysis occurred. However, hemolysis occurred when the concentration of saponins was 0.6 mg mL^{-1}, and the hemolysis rate rose rapidly with the concentration further increasing. The hemolysis rate was 55.3% when the concentration of saponins in JYH reached 1.2 mg mL^{-1}. Last but not least, the results showed that there were no significant differences in hemolysis between JYH representative compounds and SYH representative compounds in rabbit red blood cells ($P > 0.05$) (Huang et al. 2017). Additionally, *L. macranthoides* 70% ethanol extraction (5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 mg L^{-1}) and JYH extraction (0.5 g mL^{-1}) did not cause hemolysis in vitro (Wang et al. 2016; Dai et al. 2016). In brief, hemolysis of JYH and SYH may be closely related to saponins, although the hemolysis strength of saponins was not strong ($P > 0.05$). The hemolysis of SYH may be related to the inclusion of macranthoidin A **(265)** in some of its plant origins.

However, there are contrary opinions about their toxicology. SYH contains more saponins than JYH. The potential security risk of SYH should be higher than that of JYH. The release rate of β-hexosaminidase of SYH water extraction (1.46 g kg^{-1}) was higher than that of JYH water extraction (1.25 g kg^{-1}) in vitro. SYH water extraction was more likely to stimulate the degranulation of basophilic mast cells than JYH water extraction. Thereby, the allergic reaction of SYH water extraction was more severe than that of JYH water extraction (Zhang 2014). Additionally, about four hundred million patients are treated with traditional Chinese medicine injections (TCMI) in China per year. Among TCMI, intravenous SHL has the highest risk of injection-induced immediate hypersensitivity reactions (IHRs). IHRs were attributed to the intermediate fraction F2 coming from JYH and Forsythiae Fructus in SHL injection. In Gao's study, Balb/c mice were intravenously injected with the SHLI (0.5 mL/mouse), F1 (the extraction of Scutellariae Radix, 4.81 mg/mouse), or F2 (16.5 mg/mouse), respectively. Thirty minutes later, the rectal temperature was measured. F2 contributed to obvious hypothermia, while F1 has no effect on the mouse's temperature. After intravenously injecting with 5 mg mL^{-1} Evans Blue (1 mL), a representative image of Evans Blue extravasation of mouse paw was observed in F2 group. In brief, JYH for injection use exerts a safety risk (Gao et al. 2018).

In summary, JYH and SYH were found to be fairly nontoxic, for such above high concentrations no longer having toxicological meaning.

Conclusion

L. japonica (also known as JYH, honeysuckle and Rendong) was traditionally utilized for clearing heat, detoxicating and expelling exopathogenic wind-heat. According to TCM theory, the above functions are closely associated with the treatment of inflammation or various infectious diseases. From the view of TCM, JYH belongs to cold nature, and it is the main drug to cure sore, heat-toxin and seasonal febrile disease, suggesting JYH an herb of treating inflammation. In light of its long traditional use to cool blood and relieve dysentery, the relationship between the traditional use and modern therapy of JYH against virus has also been established. However, SYH is more likely for local use only. The correlation between modern usage and traditional use of SYH remains unclear. More investigations of ethnomedicinal remedies of SYH should been conducted. These findings are crucial for a better understanding of the alternative strategy of JYH and SYH and to help in the authentication of them. In brief, the traditional uses of JYH have already been substantiated by modern pharmacological studies. In Asia, JYH and SYH are often used as tea. As the above said, bioactive components (especially CGA) of them have already been deeply explored. Due to the good and positive related anti-inflammatory, antiviral and antibacterial activities, CGA was used as marker to evaluate the chemical quality of JYH and SYH. However, CGA was not specificity or even ubiquitous. Thereby employing CGA to control the quality of JYH and SYH is really exclusive or accurate? This should be studied further.

In this review, we systematically summarize knowledge on botanies, ethnopharmacology, phytochemistry, pharmacological activities, clinical use, quality control and toxicology of JYH and SYH. To date, 326 and 148 compounds have been found in JYH and SYH, respectively. phenolic acids, the major compounds presenting in JYH and SYH are similar and bioactive, with multiple bioactivities being revealed. However, reported literature showed that the main chemical differences between JYH and SYH are concentrated on saponins, such as macranthoidin A–B **(265**, **266)**, macranthoside A–B **(267**, **268)** and dipsacoside B **(269)**, and this cluster of compounds is anticipated to get more in-depth studies in anti-tumour compounds exploitation. As far as pharmacological studies of JYH and SYH, many in vitro and in vivo experiments demonstrate that they are pharmacologically similar, but also differ in some aspects. For instance, JYH is more powerful in antibacterial activity than SYH, while SYH possesses a higher intensity than JYH in antioxidative activity. What's more, neither JYH nor SYH exert significant toxicity, but some studies indicated that the hemolysis of JYH and SYH was closely related to saponins, thereby SYH showing a higher safety risk. Given that SYH contains a large amount of saponins and the toxicological mechanism remains unclear, careful consideration should be given to the use of SYH in high-risk preparations.

However, gaps still exist in the scientific studies on them. Therefore, we provide several topics which should have priority for further detailed investigation. Firstly, there are not enough phytochemistry studies on SYH. Although phenolic acids and saponins are considered as the major bioactive compounds in SYH, the investigation of other ingredients like iridoids and flavonoids is still in a shortage, which severely limited the application diversity of SYH, and the chemical difference between JYH and SYH remains unclear. Secondly, current pharmacological studies on SYH are not available to validate its difference with JYH, bringing about continuing debate. Further investigation should be performed preferentially with comparing their activity intensities in vitro and in vivo, and introduced positive control. Finally, JYH and SYH are recognized as nontoxic herbs, but few toxicological studies support the safety of them in patients with underlying diseases, especially in elderly, children and pregnant women. The potential hemolysis risk of SYH should not be ignored, and it is worth investigating its interchangeability with JYH in injection.

In conclusion, it is necessary to accelerate the phytochemistry and pharmacological studies of SYH, and figure out its difference and similarity with JYH more in-depth. Future direction of research should pay attention to accurate and rapid authentication of JYH and SYH for it is crucial to ensure the safety and function of medicinal or edible herbs as well as their preparations. Additionally, more efforts deserve to gain insights into the toxicological actions of JYH and SYH.

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