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

Yuke Li · Wen Li · Chaomei Fu · Ying Song · Qiang Fu

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Abstract Lonicerae japonicae flos (called Jinyin-hua, 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 Shanyninhua, 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

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 windbreaker 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 synonyms 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, Diervilliae, Caprifoliaceae, Linnaeae and Morinaceae) and Adoxaceae (Fan et al. 2018; Group et al. 2016). In addition, Caprifoliaceae 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).

**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/](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,  | Gray–brown to yellow–brown,  | Pale yellow–brown or yellow–brown, |
|                               |                                  | glabrous or sparse             | densely gray–white hairs      | densely yellow hairs             |
| Flower branches                | Conical-like inflorescences of   | Short raceme inflorescences,   | Short raceme inflorescences,  | Short raceme inflorescences,     |
|                               | paired flowers, densely in axils | single-paired flowers in axils | single-paired flowers in axils| 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        | Dense glandular hairs         | Densely filemot glandular hairs  |
| Medicinal part                 | Rod-shaped, slightly curved,     | orange glandular hairs         |                                |                                  |
|                               | 3–4.5 cm long, upper diameter    |                                |                                |                                  |
|                               | about 2 mm, lower 1 mm           |                                |                                |                                  |

**Fig. 1**  
* a L. japonica, b L. macranthoides, c L. hypoglauca, d L. confusa, e L. fulvotomentosa ([www.sfda.gov.cn/](http://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. mongolicus (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 | ‘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 and 1 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 highlighted.

*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   | JYH, Belamcandae Rhizoma, Coptidis Rhizoma, Astragali Radix, JYH | Curing light and moderate Type 2 diabetes                               |
| Niuhuang Jingnai | Tablet | Bovis Calculus Artifectus, 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, Taraxacherbac                                 | 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 |
| No. | Compound                        | JYH Parts | Extraction     | Reference                        | SYH Parts      | Extraction     | Origins | References                        | PubChem CID |
|-----|--------------------------------|-----------|----------------|----------------------------------|----------------|----------------|---------|-----------------------------------|-------------|
| 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)                | 9798666     |
| 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     |

**Phenolic acids**

**Chlorogenic acids derivatives common for JYH and SYH**

1. Chlorogenic acid
2. Neochlorogenic acid
3. Isochlorogenic acid A
4. Isochlorogenic acid B
5. Isochlorogenic acid C
6. Cryptochlorogenic acid
7. Cynarin
8. Methyl chlorogenate

**Chlorogenic acids derivatives only for JYH**

9. 1,5-O-Dicaffeoylquinic acid
10. 1,4-O-Dicaffeoylquinic acid
11. 5-p-Coumarylquinic acid
12. Feruloylcaffeoylquinic acid
13. Chlorogenic acid butyl ester
14. Methyl 3,5-di-O-caffeoylquinic acid
| No. | Compound                                      | JYH Parts          | Extraction | Reference                                      | SYH Parts          | Extraction | Origins | References | PubChem CID |
|-----|-----------------------------------------------|---------------------|------------|------------------------------------------------|---------------------|------------|---------|-------------|-------------|
| 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*

| No. | Compound                                      | JYH Parts          | Extraction | Reference                                      | SYH Parts          | Extraction | Origins | References | PubChem CID |
|-----|-----------------------------------------------|---------------------|------------|------------------------------------------------|---------------------|------------|---------|-------------|-------------|
| 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)                             |                     |            |         |             |             |
| No. | Compound                              | JYH Parts | Extraction Parts | SYH Parts | Extraction Parts | Origins            | References         | PubChem CID |
|-----|---------------------------------------|-----------|------------------|-----------|------------------|--------------------|--------------------|-------------|
| 32  | Butyl 5-caffeoyl quinine              | Unknown   | 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)|                    |                    |             |
| 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)|                    |                    |             |
| 38  | 4-Caffeoylshikimic acid              | Flower buds | Distilled water | 1         | Zhang et al. (2016)|                    |                    |             |
| 39  | 5-Caffeoylshikimic acid              | Flower buds | Distilled water | 1         | Zhang et al. (2016)|                    |                    |             |
| 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-cafeoylquinic acid       | Flower buds | Distilled water | 1         | Zhang et al. (2016)|                    |                    |             |
| 46  | Methyl 3-O-cafeoylquinate            | Flower buds | Distilled water | 1         | Zhang et al. (2016)|                    |                    |             |
| 47  | Methyl 1-O-cafeoylquinate            | Flower buds | Distilled water | 1         | Zhang et al. (2016)|                    |                    |             |
| 48  | Methyl 4-O-cafeoylquinate            | Flower buds | Distilled water | 1         | Zhang et al. (2016)|                    |                    |             |
| 49  | 3-Feruloyl-4-cafeoylquinic acid      | Flower buds | Distilled water | 1         | Zhang et al. (2016)|                    |                    | 91617958    |
| No. | Compound                  | JYH Parts | Extraction     | Reference | SYH Parts | Extraction | Origins | References      | PubChem CID |
|-----|---------------------------|-----------|----------------|-----------|-----------|------------|---------|-----------------|-------------|
| 50  | 3-Caffeoyl-4-feruloylquinic acid | Flower buds | Distilled water | 1         | Zhang et al. (2016) | 131752147 |
| 51  | 3-Feruloyl-5-cafeoylquinic 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-cafeoylquinic 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-caffeoylquininate | Flower buds | Distilled water | 1         | Zhang et al. (2016) | 131752148 |
| 56  | Methyl-3,4-di-O-caffeoylquininate | Flower buds | Distilled water | 1, 2      | Zhang et al. (2016), Guan et al. (2011) | 10075681  |
| 57  | Methyl-3,5-di-O-caffeoylquininate | Flower buds | Distilled water | 1, 2      | Zhang et al. (2016), Guan et al. (2011) | 10554540  |
| 58  | Methyl-1,4-di-O-caffeoylquininate | Flower buds | Distilled water | 1         | Zhang et al. (2016) | 131752148 |
| 59  | Methyl-4,5-di-O-caffeoylquininate | Flower buds | Distilled water | 1         | Zhang et al. (2016) | 131752148 |
| 60  | Methyl-1,5-di-O-caffeoylquininate | Flower buds | Distilled water | 1         | Zhang et al. (2016) | 131752148 |
| 61  | Ethyl-3,4-di-O-caffeoylquininate | Flower buds | Distilled water | 1         | Zhang et al. (2016) | 131752148 |

**Cinnamic acids derivatives common for JYH and SYH**

| No. | Compound                  | JYH Parts          | Extraction | Reference          | SYH Parts          | Extraction | Origins | References      | PubChem CID |
|-----|---------------------------|--------------------|------------|--------------------|--------------------|------------|---------|-----------------|-------------|
| 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     |
The table continues as follows:

| No. | Compound                        | JYH Parts       | Extraction       | Reference                        | SYH Parts       | Extraction       | Origins | References           | PubChem CID |
|-----|---------------------------------|-----------------|------------------|----------------------------------|-----------------|------------------|---------|-----------------------|-------------|
| 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

| No. | Compound                        | JYH Parts       | Extraction       | Reference                        | SYH Parts       | Extraction       | Origins | References           | PubChem CID |
|-----|---------------------------------|-----------------|------------------|----------------------------------|-----------------|------------------|---------|-----------------------|-------------|
| 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-hydroxycinnaminate     | 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

| No. | Compound                        | JYH Parts       | Extraction       | Reference                        | SYH Parts       | Extraction       | Origins | References           | PubChem CID |
|-----|---------------------------------|-----------------|------------------|----------------------------------|-----------------|------------------|---------|-----------------------|-------------|
| 79  | 1-O-Dimethoxycinnamoylquinic    | Flower buds     | Distilled water  | 1                                |                 |                  |         |                       |             |
| 80  | 3-O-Dimethoxycinnamoylquinic    | Flower buds     | Distilled water  | 1                                |                 |                  |         |                       |             |
| 81  | 4-O-Dimethoxycinnamoylquinic    | Flower buds     | Distilled water  | 1                                |                 |                  |         |                       |             |
| No. | Compound | JYH Parts | Extraction | Reference | SYH Parts | Extraction | Origins | References | PubChem CID |
|-----|----------|-----------|------------|-----------|-----------|------------|---------|------------|-------------|
| 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) | |
| 83  | Vanillic acid | Flower buds | Ethanol | Lee et al. (2010a) | |
| 84  | Vanillic acid 4-O-β-D-(6-O-benzoylglucopyranoside) | Flower buds | Ethanol | Lee et al. (2010a) | |
| 85  | Vanillic acid 4-O-β-D-(6-O-benzoylpyranoside) | Flower buds | Ethanol | Lee et al. (2010a) | |
| 86  | Protocatechuic acid | Flowers | Methanol | Choi et al. (2007) | |
| 87  | 4-Hydroxybenzoic acid | Flower buds | Ethanol | Li and Li (2005) | |
| 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 |
| 96  | Chrysoeriol | Dried flowers | Methanol | Choi et al. (2007) | |
| 97  | Rhoifolin | Aerial parts | Methanol | Son et al. (1992) | |
| 98  | Flavoyadorinin B | Flower buds | Ethanol | Lee et al. (2010a) | |
| No. | Compound                        | JYH Parts | Extraction | Reference | SYH Parts | Extraction | Origins | References | PubChem CID |
|-----|--------------------------------|-----------|------------|-----------|-----------|------------|---------|-------------|-------------|
| 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'-Trimethoxyflavone | 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',S'-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-glucopyranoside | Flowers/Flower buds | 30% ethanol | Zhen (2010) |           |            |         |             |             |
| No. | Compound                      | JYH Parts                  | Extraction     | Reference          | SYH Parts                  | Extraction     | Origins | References                  | PubChem CID |
|-----|-------------------------------|----------------------------|----------------|--------------------|----------------------------|----------------|---------|------------------------------|-------------|
| 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*

| No. | Compound                      | JYH Parts                  | Extraction     | Reference          | SYH Parts                  | Extraction     | Origins | References                  | PubChem CID |
|-----|-------------------------------|----------------------------|----------------|--------------------|----------------------------|----------------|---------|------------------------------|-------------|
| 124 | Chrysoeriol-7-O-xyloside       | Flower buds                | n-butanol      | Hu et al. (2016)   |                            |                |         |                              |             |

*Flavonols common for JYH and SYH*

| No. | Compound                      | JYH Parts                  | Extraction     | Reference          | SYH Parts                  | Extraction     | Origins | References                  | PubChem CID |
|-----|-------------------------------|----------------------------|----------------|--------------------|----------------------------|----------------|---------|------------------------------|-------------|
| 125 | Rutin                         | Unknown                    | Unknown        | Chang and Hsu (1992)| Flower buds                | n-butanol      | 1, 4    | Chai et al. (2004c), Chai et al. (2004a) | 5280343     |
| 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 | Unknown                      | 5282102     |
| 128 | Isoquercurtin                 | Aerial parts               | Methanol       | Son et al. (1992)  | Flower buds                | Ethyl acetate  | 1       | Jia et al. (2008)             | 5280804     |
| 129 | Isohorhamnetin 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*

| No. | Compound                      | JYH Parts                  | Extraction     | Reference          | SYH Parts                  | Extraction     | Origins | References                  | PubChem CID |
|-----|-------------------------------|----------------------------|----------------|--------------------|----------------------------|----------------|---------|------------------------------|-------------|
| 131 | 3-Methoxyluteolin             | Flower buds                | Acetone        | Feng et al. (2011) |                            |                |         |                              |             |
| 132 | Isohorhamnetin 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)          |                            |                |         |                              |             |
| No. | Compound | JYH parts | SYH parts | Extraction | PubChem CID |
|-----|-----------|-----------|-----------|------------|------------|
| 135 | Quercetin-7-O-b-D-glucopyranoside | Flowers/Flower buds | Flowers/Flower buds | n-butyl alcohol | 5282160 |
| 136 | Quercetin 3-O-hexoside | Leaves/Flowers/Stems | Leaves/Flowers/Stems | 70% methanol | 5489114 |
| 137 | Kaempferol | Flowers/Flower buds | Flowers/Flower buds | Ethyl acetate | 5280865 |
| 138 | Flavone | Aerial parts | Aerial parts | Ethyl acetate | 5489114 |
| 139 | Eriodictyol | Aerial parts | Aerial parts | Ethyl acetate | 5489114 |
| 140 | 3-O-Methyl loniflavone [5,5',7,7',3'-tetrahydroxy 4',4'-biflavonyl ether] | Leaves | Leaves | 80% methanol | 440735 |
| 141 | Loniflavone [5,5',7,7',3'-pentahydroxy 4',4'-biflavonyl ether] | Leaves | Leaves | 80% methanol | 440735 |
| 142 | Loganin | Flowers | Flowers | Ethyl acetate | 87691 |
| 143 | Sweroside | Flowers/Flower buds | Flowers/Flower buds | Ethanol | 1, 2, 3, 4 |
| 144 | Secologanoside | Flower buds | Flower buds | Ethanol | 644698 |
| 145 | Ethyl secologanoside | Flower buds | Flower buds | Ethanol | 644698 |
| 146 | Centaurin | Leaves/Flowers buds/Stems | Flower buds | Ethanol | 443343 |
| 147 | 7-Epiloganin | Flower buds | Flower buds | Ethanol | 443343 |
| No. | Compound                      | JYH Parts   | JYH Extraction | Reference                              | SYH Parts   | SYH Extraction | Origins | SYH References | PubChem CID |
|-----|-------------------------------|-------------|----------------|----------------------------------------|-------------|----------------|---------|----------------|-------------|
| 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 | Kingside                      | 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)                    |             |                |         |                 |             |
| No. | Compound                     | JYH Parts | JYH Extraction | SYH Parts | SYH Extraction | Reference                  | Origins | References | PubChem CID |
|-----|------------------------------|-----------|----------------|-----------|----------------|----------------------------|---------|------------|-------------|
| 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)           |         |            |             |
| 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-Glucopyranosyl-3-methoxy-benzoyl) secologanolic acid | Stems/leaves | Methanol       |           |                | Machida et al. (2003)       |         |            |             |
| 184 | 6’-O-(7α-Hydroxyxwersosyloxy) loganin | Stems/leaves | Methanol       |           |                | Machida et al. (2003)       |         |            | 45783101    |
| 185 | (E)-Aldosecologanin          | Stems/leaves | Methanol       |           |                | Machida et al. (2003)       |         |            |             |
| 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      |
| No. | Compound                                      | JYH Parts    | JYH Extraction | Reference                        | SYH Parts    | SYH Extraction | Origins     | References                  | PubChem CID |
|-----|-----------------------------------------------|--------------|----------------|----------------------------------|--------------|----------------|-------------|-----------------------------|-------------|
| 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-Acetyllecoxylloganin                     | 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-Glcopyranosylharpagoside              | Dried flower buds | 75% ethanol  | Liu et al. (2015)                |              |                |             |                              |             |
| No. | Compound                                      | JYH Parts            | SYH Parts            | Reference               | SYH Extraction Parts | SYH Extraction | Origins | SYH References | PubChem CID |
|-----|-----------------------------------------------|----------------------|----------------------|-------------------------|----------------------|-----------------|----------|----------------|------------|
| 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             | Liu et al. (2012)       |                      |                 |          |                |            |

**Saponins**

| No. | Compound                                             | JYH Parts | SYH Parts | Reference               | SYH Extraction Parts | SYH Extraction | Origins | SYH References | PubChem CID |
|-----|------------------------------------------------------|-----------|-----------|-------------------------|----------------------|----------------|----------|----------------|------------|
| 235 | α-Hederin                                            | Flower buds | Ethanol   | Chen et al. (2000)      | Unknown              | Unknown         | Unknown  | Unknown         | Chen et al. (2000) |
| 236 | Loniceroside A                                       | Aerial parts | Methanol | Ho Son et al. (1994)    | Flowers/Flower buds | Ethyl acetate   | Unknown  | Unknown         | Lin et al. (2008)  |
| 237 | Loniceroside B                                       | Aerial parts | Methanol | Ho Son et al. (1994)    | Flowers/Flower buds | Ethyl acetate   | Unknown  | Unknown         | Lin et al. (2008)  |
| No. | Compound                                      | JYH Parts          | Extraction   | Reference                  | SYH Parts          | Extraction   | Origins     | References            | PubChem CID |
|-----|-----------------------------------------------|--------------------|--------------|----------------------------|--------------------|--------------|-------------|------------------------|-------------|
| 238 | Loniceroside C                               | Aerial parts       | Butanol      | Kwak et al. (2003)          | Flowers/Flower buds | Ethyl acetate | Unknown    | Lin et al. (2006)       |             |
| 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-Rhamnopyranosyl(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)            |                    |              |            |                        | 482163      |
| 249 | Saponin 4                                    | Flower buds        | Methanol     | Qi et al. (2009)            |                    |              |            |                        |             |
| 250 | Daucosterol                                  | Flowers/Flower buds | Ethyl acetate | Wang et al. (2013a)         |                    |              |            |                        | 5742590     |
| 251 | Oleanolic acid 28-α-L-rhamnopyranosyl-(1→2)-β-D-xylpyranosyl(1→6)-β-D-glucopyranosyl ester | Flowers            | Methanol     | Choi et al. (2007)          |                    |              |            |                        |             |
| No. | Compound                                                                 | JYH Parts | Extraction | Reference          | SYH Parts | Extraction | Origins | References | PubChem CID |
|-----|--------------------------------------------------------------------------|-----------|------------|--------------------|-----------|------------|---------|-------------|-------------|
| 252 | Hederagenin-3-O-α-L-rhamnopyranosyl→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-Rhamnopyranosyl(1→2)-α-L-arabinopyranosyl-28-O-β-D-glucopyranosyl hederagenin | Aerial parts | Methanol   | Kawai et al. (1988) |           |            |         |             |             |
| 255 | 3-O-α-L-Rhamnopyranosyl(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-Arabinopyranosyl hederagenin 28-O-β-D-rahmnoypyransyl(1→2) [β-D-xylopyranosyl(1→6)-β-D-glucopyranosyl ester] | Flower buds | 95% ethanol | Lou et al. (1996) |           |            |         |             |             |
| 257 | 3-O-α-L-Rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl hederagenin 28-O-β-D-xylopyranosyl(1→6)-β-D-glucopyranosyl ester | Flower buds | 95% ethanol | Lou et al. (1996) |           |            |         |             |             |
| 258 | 3-O-α-L-Rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl hederagenin 28-O-β-D-Rhamnopyranosyl(1→2) [β-D-xylopyranosyl(1→6)-β-D-glucopyranosylester] | Flower buds | 95% ethanol | Lou et al. (1996) |           |            |         |             |             |
| No. | Compound                                                                 | JYH Parts | Extraction | Reference               | SYH Parts | Extraction | Origins | References     | PubChem CID |
|-----|---------------------------------------------------------------------------|-----------|------------|-------------------------|-----------|------------|---------|----------------|-------------|
| 259 | 3-**O-β-D-Glucopyranosyl**-(1 → 4) **-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)      |           |            |         |                 |             |
| 260 | 3-**O-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)      |           |            |         |                 |             |
| 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-arabinopyranosyl 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-arabinopyranosyl hederagenin**28-**O-β-D-xylopyranosyl**(1 → 6)-**β-D-glucopyranosyl ester** | Flower buds | Ethanol    | Chen et al. (2000)      |           |            |         |                 |             |
| No. | Compound          | JYH Parts | Extraction       | Reference                                                                 | SYH Parts | Extraction       | Origins                     | References                                                                 | PubChem CID |
|-----|-------------------|-----------|------------------|---------------------------------------------------------------------------|-----------|------------------|-----------------------------|----------------------------------------------------------------------------|-------------|
| 265 | Macranthoidin A   | Flowers   | Ethanol          | Ren et al. (2008), Mao et al. (1993)                                     | 1, 2, 3, 4| Ethanol          | 1                           | Ren et al. (2008), Mao et al. (1993)                                    | 14564503    |
| 266 | Macranthoidin B   | Flowers   | Ethanol          | Ren et al. (2008), Mao et al. (1993)                                     | 1, 2, 3, 4| Ethanol          | 1                           | Ren et al. (2008), Mao et al. (1993)                                    | 119025667   |
| 267 | Macranthoside B   | Flowers   | Ethanol          | Chai et al. (2005), Mao et al. (1993)                                    | 1, 3, 4   | Ethanol          | 1                           | Chai et al. (2005), Mao et al. (1993)                                    | 135396862   |
| 268 | Macranthoside A   | Flowers   | Ethanol          | Chai et al. (2005), Mao et al. (1993)                                    | 1, 3, 4   | Ethanol          | 1                           | Chai et al. (2005), Mao et al. (1993)                                    | 176534      |
| 269 | Dipsacoside B     | Flowers   | Ethanol          | Ren et al. (2008), Mao et al. (1993)                                     | 1, 2, 3, 4| Ethanol          | 1                           | Ren et al. (2008), Mao et al. (1993)                                    | 21627940    |
| 270 | Dipsacoside VI    | Unknown   | Unknown          | Huang et al. (2017)                                                      | Unknown   | Unknown          | Unknown                     | Huang et al. (2017)                                                      |             |
| 271 | Hederagenin-3-O-α-L-arabinopyranosyl (2 → 1)-O-α-L-rhamnopyranoside | Flowers | Methanol         | Chai et al. (2005)                                                      | 1, 3, 4   | Methanol         | 1                           | Chai et al. (2005)                                                      |             |
| 272 | Hederagenin-28-O-β-D-glucopyranosyl (6 → 1)-O-β-D-glucopyranosyl ester | Flower buds | 50% methanol | Chen et al. (2007)                                                      | 1         | 50% methanol     | 1                           | Chen et al. (2007)                                                      |             |
| 273 | Thalictoside VI   | Flower buds | 70% ethanol | Chen et al. (2015a)                                                     | 1         | 70% ethanol      | 1                           | Chen et al. (2015a)                                                     | 23815408    |
| 274 | Asiatic acid      | Flower buds | 70% ethanol | Chen et al. (2015a)                                                     | 1         | 70% ethanol      | 1                           | Chen et al. (2015a)                                                     | 119034      |
| 275 | Leiyemudanoside A | Flower buds | Methanol        | Liu et al. (2013)                                                       | 1         | Methanol         | 1                           | Liu et al. (2013)                                                       |             |
| 276 | Lonimacranthoide I | Flower buds | 50% ethanol | Chen et al. (2012a)                                                    | 1         | 50% ethanol      | 1                           | Chen et al. (2012a)                                                    |             |
| 277 | Lonimacranthoide II | Flower buds | 50% ethanol | Chen et al. (2012a)                                                   | 1         | 50% ethanol      | 1                           | Chen et al. (2012a)                                                   |             |
| 278 | Lonimacranthoide III | Flower buds | 50% ethanol | Chen et al. (2008b)                                                   | 1         | 50% ethanol      | 1                           | Chen et al. (2008b)                                                   |             |
| 279 | Lonimacranthoide IV | Flower buds | Ethanol       | Yu et al. (2012)                                                       | 1         | Ethanol          | 1                           | Yu et al. (2012)                                                       |             |
| No. | Compound | JYH Parts | JYH Extraction | SYH Parts | SYH Extraction | Origins | References | PubChem CID |
|-----|----------|------------|----------------|-----------|----------------|--------|------------|------------|
| 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) |
| 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 ester | 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) |
| No. | Compound                                      | JYH Parts | JYH Extraction | SYH Parts | SYH Extraction | Origins | Reference(s)               | PubChem CID |
|-----|-----------------------------------------------|-----------|----------------|-----------|----------------|---------|-----------------------------|-------------|
| 289 | 3-O-β-D-Glucopyranosyl-                      |           |                |           |                | Flower buds | Methanol | Liu et al. (2013)            |             |
|     | (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                   |           |                |           |                |          |                              |             |
|     | **Essential oils**                           |           |                |           |                |          |                              |             |
| 290 | 9,12,15-Octadecatrienoic acid methyl ester   | Flowers   | Absolute ether |           | Flower buds   | Distilled water | 1       | Wu et al. (2015a)            | 9316        |
| 291 | Hexadecane                                   | Flowers   | Absolute ether |           | Flower buds   | Ethyl acetate | 1       | Wu et al. (2015a)            | 11006       |
| 292 | Nonadecane                                   | Flowers   | Absolute ether |           | Flower buds   | Distilled water | 1       | Wu et al. (2015a)            | 12401       |
| 293 | Dibutyl phthalate                            | Flowers/Flower buds | Absolute ether |           | Flower buds   | Distilled water | 1       | Wu et al. (2015a)            | 3026        |
| 294 | Hexadecanoic acid methyl ester              | Flowers   | Absolute ether |           | Flower buds   | Distilled water | 1       | Wang et al. (1999)           | 8181        |
| 295 | Linalool                                     | Flowers/Flower buds | Absolute ether |           | Flower buds   | Ethyl acetate | 1       | Tong et al. (2005)           | 6549        |
| 296 | Octadecanal                                  | Flowers   | Absolute ether |           | Flower buds   | Distilled water | 1       | Wang et al. (2009c)          | 12533       |
| 297 | Phytool                                      | Flowers   | Absolute ether |           | Flower buds   | Distilled water | 1       | Wang et al. (2009c)          | 5280435     |
| 298 | α-Terpineol                                  | Flowers   | Absolute ether |           | Flower buds   | Distilled water | 1       | Wang et al. (2009c)          | 17100       |
| 299 | 5-(Prop-2-enoyloxy)pentadecane               | Flowers   | Absolute ether |           | Flower buds   | Distilled water | 1       | Wang et al. (2009c)          | 543288      |
| 300 | Eicosane                                     | Flowers   | Absolute ether |           | Flower buds   | Distilled water | 1       | Wang et al. (2009c)          | 8222        |
| 301 | Triacontane                                  | Flowers   | Absolute ether |           | Flower buds   | Distilled water | 1       | Wang et al. (2009c)          | 12535       |
| 302 | 2,6,10-Trimethyltetradecane                 | Flowers   | Absolute ether |           | Flower buds   | Distilled water | 1       | Wang et al. (2009c)          | 85785       |
| 303 | Octadecane                                   | Flowers   | Absolute ether |           | Flower buds   | Distilled water | 1       | Wang et al. (2009c)          | 11635       |
| No. | Compound                        | JYH Parts | SYH Parts | JYH Reference       | SYH Reference       | PubChem CID |
|-----|---------------------------------|-----------|-----------|---------------------|---------------------|-------------|
| 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 | α-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) |                     | 5472209     |
| 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)   |                     | 20490       |
| 324 | Aromadendrene                   | Unknown   | Unknown   | Wang (2010)         |                     | 91354       |
| 325 | Geraniol                        | Unknown   | Unknown   | Wang (2010)         |                     | 637566      |
| 326 | (Z)-Jasmonate                   | Flowers   | Hexane    | Ikeda et al. (1994) |                     | 1549018     |
| 327 | (Z)-Jasmin lactone              | Flowers   | Hexane    | Zhang (2014)        |                     | 5281929     |
| 328 | Methyl jasmonate                | Flowers   | Hexane    | Zhang (2014)        |                     | 5367719     |
| 329 | Methyl epi-jasmonate            | Flowers   | Hexane    | Zhang (2014)        |                     | 5367719     |
| 330 | Benzaldehyde                     | Flowers/Stems/Leaves | Distilled water | Wu et al. (2009) |                     | 240         |
| No. | Compound                        | JYH Parts          | Reference  | SYH Parts          | Extraction | Origins | References          | PubChem CID |
|-----|---------------------------------|--------------------|------------|--------------------|------------|---------|----------------------|-------------|
| 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 | Cyclohexylisoxalic ester        | Flowers            | Diethyl ether | Du et al. (2009)  |            |         |                      |             |
| 335 | Methylecyclohexane              | Flowers            | Diethyl ether | Du et al. (2009)  |            |         |                      |             |
| 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       |
| No. | Compound                                      | SYH Parts | SYH Extraction | Origins | SYH References | PubChem CID |
|-----|-----------------------------------------------|-----------|----------------|---------|----------------|-------------|
| 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) | 3650815     |
| 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       | SYH       | Origins      | References     | PubChem CID |
|-----|---------------------------------------|-----------|-----------|--------------|----------------|-------------|
|     |                                       | 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) | Flower buds | Distilled water | 1 | Wu et al. (2015a) | 7800     |
| 378 | Nonacontane                           | Flower buds | Unknown | Wang (2008) | Flower buds | Distilled water | 1 | Wu et al. (2015a) | 18980672 |
| 379 | 2(E)-3-ethoxyacrylic acid             | Flowers/Flower buds | Chloroform | Bi et al. (2007) | Flower buds | Distilled water | 1 | Wu et al. (2015a) | 5709609  |
|     | Phenols                                |           |           |              |                |             |
| 380 | Lonicerjaponin A                      | Flower buds | Methanol | Kashiwada et al. (2013) | Flower buds | Methanol | Kashiwada et al. (2013) | 102497708 |
| 381 | Lonicerjaponin B                      | Flower buds | Methanol | Kashiwada et al. (2013) | Flower buds | Methanol | Kashiwada et al. (2013) | 102497709 |
| 382 | 3,4-Dihydroxybenzaldehyde             | Flowers/Flower buds | Alcohol | Huang et al. (1996) | Flower buds | Alcohol | Huang et al. (1996) | 8768     |
| No. | Compound                        | JYH Parts       | Extration     | Reference                  | SYH Parts       | Extraction     | Origins       | References                  | PubChem CID |
|-----|---------------------------------|-----------------|---------------|----------------------------|-----------------|---------------|---------------|----------------------------|-------------|
| 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-Benzentriol               | 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 | Lonijaponinicotinonesides A      | Flower buds     | Distilled water | Jiang et al. (2015) |                 |               |               |                            |             |
| 394 | Lonijaponinicotinonesides B      | Flower buds     | Distilled water | Jiang et al. (2015) |                 |               |               |                            |             |
| 395 | (+)-N-(3-Methylbut-2-enoyl-β-D-glucopyranosyl)-nicotinate | Flower buds | Distilled water | Song (2008) |                 |               |               |                            |             |
| 396 | (+)-N-(3-Methylbut-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      |
| No. | Compound                                                                 | JYH Parts | Extraction   | Reference | SYH Parts | Extraction | Origins | References | PubChem CID |
|-----|---------------------------------------------------------------------------|------------|--------------|-----------|------------|------------|---------|-------------|-------------|
| 401 | Sucrose                                                                   | Flower buds| 70% ethanol  | Lee et al. (2010b) |           |            |         |             | 5988        |
| 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) |           |            |         |             |             |
| 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-Dimethoxyphenylpropenoic 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-Hydroxyphenylglycerol 9-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) |           |            |         |             |             |
| No. | Compound                                      | JYH      | SYH      | Origin          | Reference                                                                 |
|-----|-----------------------------------------------|----------|----------|-----------------|---------------------------------------------------------------------------|
|     |                                               | Parts    | Extraction |                 |                                                                           |
| 411 | Benzyl 2-O-β-D-glucopyranosyl-2, 6-dihydroxy benzoate | Flowers/Flower buds | Ethyl acetate | Flowers/Flower buds | Wang et al. (2013a)                                                         |
| 412 | Gentisic acid 5-O-β-D-glucopyranoside          | Flowers/Flower buds | Ethyl acetate | Flowers/Flower buds | Wang et al. (2013a)                                                         |
| 413 | Eugenyl β-D-glucopyranoside                    | Flowers/Flower buds | Ethyl acetate | Flowers/Flower buds | Wang et al. (2013a)                                                         |
| 414 | Eugenyl β-D-xylopyranosyl-(1→6)-β-D-glucopyranoside | Flowers/Flower buds | Ethyl acetate | Flowers/Flower buds | Wang et al. (2013a)                                                         |
|     | **Miscellaneous**                              |          |          |                 |                                                                           |
| 415 | 2-Butanol                                      | Unknown  | Unknown  | Unknown         | Wang et al. (2009c)                                                       |
| 416 | 1-O-Methyl-myo-inositol                        | Flower buds | Unknown | Unknown         | Wang (2008)                                                               |
| 417 | Syringin                                       | Flowers/Flower buds | Distilled water | Flowers/Flower buds | Yu et al. (2015b)                                                          |
| 418 | Coniferin                                      | Roots    | 95% ethanol | Unknown         | Jin-qian et al. (2016)                                                    |
| 419 | 5-Hydroxymethyl-2-furfural                     | Flowers/Flower buds | Methanol | Flowers/Flower buds | Choi et al. (2007)                                                        |
| 420 | Shuangkangsu                                   | Flowers  | Unknown  | Unknown         | Wang (2008)                                                               |
| 421 | Citric acid                                    | Flowers/Flower buds | Distilled water | Flowers/Flower buds | Zhang et al. (2012)                                                        |

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).

![Phenolic acids](image)

*Fig. 2* The major phenolic acids 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
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 (tmax = 0.58 ± 0.13 h, Cmax = 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. t₁/₂ of i.v, i.m and i.g administration were 0.44, 0.50 and 0.38 h, and AUC₀⁻→∞ 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, tmax = 0.1 h, Cmax = 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.
Fig. 5 The chemical structures of main saponins in SYH

Macranthoidin A

Macranthoside B

Macranthoidin B

Macranthoside A

Dipsicoside B

Loniceroside A
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, diabetes 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-
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), 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 (IC₅₀) values of 6.8–11.6 µM. The positive control, oseltamivir, gave an IC₅₀ 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 (IC₅₀ = 20.07 ± 0.37 µM), with IC₅₀ values of 7.96 ± 0.47 and 12.60 ± 1.50 µM, respectively.

| Compound | Extraction | JYH | SYH | Refs |
|----------|------------|-----|-----|------|
| L. macranthoides | Methanol | 2.931 ± 0.010 | 5.657 ± 0.010 | Yang et al. (2016) |
| L. hypoglauca | Methanol | 0.472 ± 0.010 | 0.060 ± 0.010 | Zhang et al. (2015) |
| L. confusa | Methanol | 0.951 ± 0.008 | 0.081 ± 0.003 | Xiong et al. (2005) |
| L. fulvotomentosa | Methanol | 0.093 ± 0.001 | nd | Xiong et al. (2005) |
| 70% methanol | nd | 0.242 ± 0.010 | 0.120 ± 0.010 | Li et al. (2003), Zhang et al. (2015) |
| 70% methanol | nd | 0.242 ± 0.010 | 0.120 ± 0.010 | Zhang et al. (2015) |
| 70% methanol | nd | 0.242 ± 0.010 | 0.120 ± 0.010 | Zhang et al. (2015) |
| 70% methanol | nd | 0.242 ± 0.010 | 0.120 ± 0.010 | Zhang et al. (2015) |
| 70% methanol | nd | 0.242 ± 0.010 | 0.120 ± 0.010 | Zhang et al. (2015) |
| 70% methanol | nd | 0.242 ± 0.010 | 0.120 ± 0.010 | Zhang et al. (2015) |
| 70% methanol | nd | 0.242 ± 0.010 | 0.120 ± 0.010 | Zhang et al. (2015) |

tr trace, nd not detect, nr no record
| Effect                  | Origins | Compounds | Model/targets | Positive control | Formulation/dosage | Result/mechanism/method | References         |
|-------------------------|---------|-----------|---------------|------------------|--------------------|--------------------------|---------------------|
| Anti-inflammatory activity | JYH     | 1–6, 62, 69 | LPS-induced macrophage | Reference compounds prednisolone showed potent inhibition of 57.9% NO production, TNF-α and IL-6 secretion | 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 | In vivo, 100 mg kg⁻¹ | Inhibited ear edema 31% | Kwak et al. (2003) |
|                         |         | 1        | RAW264.7 macrophages | The presence of Indomethacin only produced a significant reduction | In vitro, 10 and 100 μmol L⁻¹ | Inhibited mRNA expression and COX-2 activity in a dose-dependent manner. Only high concentration of 100 μmol L⁻¹ reduced COX-1 expression | Guan et al. (2014a) |
|                         |         | 281      | LPS-activated RAW264.7 cells | Betamethasone, 30 μmol L⁻¹ only produced a significant reduction of COX-2 mRNA expression | In vitro, 30 μmol L⁻¹ | Inhibited expression of pro-inflammatory proteins iNOS and NO releasing | Mei et al. (2019) |
| Bacteriostatic activity | JYH     | 1, 4      | P. aeruginosa | Lamivudine | In vitro, 0.14 to (1000) μg L⁻¹ | The most correlated compounds against antibacterial activities assayed by canonical correlation analysis | Shi et al. (2016) |
|                         | SYH     |           |               |                   |                    |                          |                     |
| 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 | Lamivudine | In vitro | 1 and 62 inhibited HBsAg secretion at an IC₅₀ value of 242 μM and 13 μM, but showed little inhibition of HBeAg secretion at a dose up to (1000) μM | Wang et al. (2009a) |
|                         |         |           |               |                   |                    |                          |                     |
|                         | JYH     | 1–4, 6   | H1N1 virus | Ribavirin, 20 mg kg⁻¹ | In vitro |                          |                                 |
|                         |         |           |               |                   |                    |                          |                                 |
|                         | JYH     | 148, 200 | H1N1 virus | Oseltamivir carboxylate, 100 μg mL⁻¹ | 45.5% inhibition | 148 and 200 had inhibitory activities against H1N1 replication inhibitory rates were 53.1% and 49.3%, respectively | Kashiwada et al. (2013) |
| 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                              | Inhibited cell growth of six cancer cell lines, especially human acute promyelocytic leukaemia HL-60 cells, with an IC<sub>50</sub> 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                              | induced apoptosis and autophagy via reactive oxygen species ROS which could activate caspase-3 and caspase-9, cleave polyadenosinediphosphate-ribose polymerase, regulate adenylate-activated protein kinase, and inhibited mammalian target of rapamycin. Inhibits 70% colony formation at the concentration of 20 μmol L<sup>-1</sup> | Shan et al. (2016) |
|                        | 1       | 267       | Human hepatoma HepG2 cells                                                   |                                                                                                           | In vitro                              | In vitro With concentration increasing, the inhibitory rates increased 2.58, 23.21, 55.89, 86.55 and 98.14%, with IC<sub>50</sub> value of 10.10 ± 0.93 μM | Wang et al. (2009b) |
|                        | 1       | 267       | Female athymic BALB/c nude mouse                                              |                                                                                                           | In vivo                                | The volume and weight of xenograft tumors in mice were decreased remarkably \( P < 0.05 \) |                                                                                       |            |

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 IC50 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). Lonicerose C (238), 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

Fig. 7 Proposed molecular mechanisms of anti-tumour activity 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

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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 \(\alpha\)-L-Rhap-(1 \rightarrow 2)-\(\alpha\)-L-Arap 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-\(\alpha\), 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-\(\alpha\), nuclear factor (NF)-\(\kappa\)B, IL-(1\(\beta\), 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-
| Effect                         | Origins          | Extracts            | Model                                | Formulation/dosage | Result/method                                                                 | Reference                  |
|-------------------------------|------------------|---------------------|--------------------------------------|--------------------|--------------------------------------------------------------------------------|----------------------------|
| Anti-inflammatory activity    | JYH              | Water               | Trypsin-induced mast cell            | In vitro           | 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           | 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           | 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 | In vivo            | 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, inhibits 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 SYH                   | 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 | Inhibits 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 Salmonella anatum (intensity: E. coli > S. aureus > B. cereus > S. anatum > L. monocytogenes) | Shan et al. (2007)        |
|                             |         |          |            |                     | Gram-positive bacteria are generally more sensitive than Gram-negative bacteria to JYH |                           |
|                             |         |          |            | 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.                   | 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     |          | 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)       |
|                             |         |          |            |                     | Liver fibrosis is significantly reduced                                         | Sun et al. (2010)         |
|                             | 2       |          | In vivo    | 200 mg mL\(^{-1}\) | Enhances the detoxification of liver to AM and alleviates mouse liver injury   | Shi and Liu (1995)        |
|                             | JYH and SYH |      | In vivo    | 100 mg kg\(^{-1}\) | Decrease serum glutamic-pyruvic transaminase, liver triglyceride and MDA levels significantly (\(P < 0.05\)) | Tang et al. (2016)        |
| 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\(^{-}\) and -OH effectively.                                                      | Wu et al. (2015b), Xu et al. (2014) |
| Hypoglycemic activity  | JYH     | polysaccharides           | STZ-induced diabetic rats       | In vivo            | 800 mg kg\(^{-1}\)                                                                                   | Wang et al. (2017a), Zhao et al. (2018) |
|                        | SYH     | polysaccharide            | STZ-induced diabetic rats       | In vivo            | 800 mg kg\(^{-1}\)                                                                                   |                          |
|                        |         | Administered orally       |                                |                    |                                                                                                    |                          |
| Anti-tumour activity   | JYH     | polyphenolic              | Human hepatoma HepG2 cell line  | In vitro           | 10 mg mL\(^{-1}\)                                                                                   | Park et al. (2012a)      |

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

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) could 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 δ-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 (H₂O₂-induced) oxidative injury endothelial cells and cardiomyocytes by methyl thiazolyl tetrazolium assay. The scavenging rates of superoxide anion free radical (O₂⁻) 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 pre-treating, the survival rates of H₂O₂-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 O₂⁻· 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 O₂⁻· 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)-induced 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, total triglyceride, 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 activities 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 secretary 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$_{an}$ (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

| 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 | Hydrodistillation is the best choice to extract pure volatile fraction Ethyl acetate fraction exhibited the highest content of total phenolic acids and total flavonoids | Yang et al. (2017b), Kong et al. (2017) |
| Extraction methods | Extraction yields of phenolic acids in JYH are associated with ethanol concentration | | 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 \(\beta\)-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 JYH 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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