Rubus chingii Hu: A Review of the Phytochemistry and Pharmacology

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Rubus chingii Hu (R. chingii), referred to as “Fu-Pen-Zi” in Chinese, has great medicinal and dietary values since ancient times. The dried fruits of R. chingii have been widely used in traditional Chinese medicine (TCM) for the treatment of kidney enuresis and urinary frequency for centuries. According to current findings, R. chingii has been reported to contain a variety of chemical constituents, mostly triterpenoids, diterpenoids, flavonoids, and organic acids. These compounds have been demonstrated to be the major bioactive components responsible for pharmacological effects such as anticomplementary, anticancer, antioxidant, antimicrobial, and anti-inflammatory functions. Therefore, this review focused on the up-to-date published data of the literature about R. chingii and comprehensively summarized its phytochemistry, pharmacology, quality control, and toxicity to provide a beneficial support to its further investigations and applications in medicines and foods.

Keywords: Rubus chingii Hu, phytochemistry, pharmacology, toxicity, quality control

INTRODUCTION

The genus Rubus, belonging to the Rosaceae family, has edible and economically important fruits and is widely distributed throughout the Northern Hemisphere (Moreno-Medina et al., 2018). This genus consists of over 700 species, about 194 of which occur in China, including R. chingii, R. idaeus, R. rosifolius, R. parvifolius, and so on (Li et al., 2015). Among them, R. chingii is an important functional food with the fruits known as “Fu-Pen-Zi” in Chinese. It is mainly cultivated in East China, especially in Jiangxi province, Anhui province, Jiangsu province, Zhejiang province, and Fujian province. Due to its rich nutritional and medicinal value, R. chingii has been frequently used in traditional Chinese medicine (TCM) for centuries (Liu and Niu, 2014). The medical properties of R. chingii have been mentioned in many landmark Chinese medical monographs, such as “Compendium of Materia Medica,” “Bencao Mengquan,” “Leigong Paozhi Lun,” and “Qianjin Yi Fang.” According to the theory of traditional Chinese herbal medical science, R. chingii is commonly used as a tonic for the treatment of enuresis, kidney deficiency, impotence and spermaemia, frequency of micturition, spermatorrhea, and other illnesses (Xie et al., 2013a).

Since the universal uses of R. chingii in folk medicines, a great deal of studies concerning the chemical constituents and pharmacological activities of this medicinal plant have been carried out, which gave rise to numerous interesting and attractive results. Many in vitro and in vivo investigations have indicated that the extracts and the ingredients isolated from R. chingii possess abundant pharmacological effects, such as anticomplementary, anticancer, antioxidant, antimicrobial, anti-aging and anti-inflammatory activities (Shi, 2017). These marvelous biological functions of this herb can be attributed to the presence of a broad spectrum of phytochemical constituents including triterpenoids, diterpenoids, flavonoids, organic acids, and many other compounds.
Although some brief reviews about the chemical constituents and biological activities have been conducted, these papers were written in Chinese and not studied in a systematic manner. This paper strives for a comprehensive overview of the latest information on the phytochemistry, biological activities, quality control, as well as the toxicity of this herb. More importantly, the correlation between the biological properties and the existence of the bioactive chemical components responsible for the actions has also been discussed based on the published literatures. Finally, the major achievements and shortcomings, together with the possible tendency and perspective for future food and pharmacological research of this herb, have been put forward, too. We believe that this review will highlight the significance of *R. chingii* and indicate new research directions of this species.

**PHYTOCHEMICAL CONSTITUENTS OF R. CHINGII**

So far, more than 235 chemical constituents have been isolated and identified from *R. chingii* (Table 1). These compounds include 15 triterpenoids, 15 diterpenoids, 18 flavonoids, 7 alkaloids, 95 volatile compounds, 5 coumarins, 9 steroids, 56 organic acids, and 15 other compounds. Among them, triterpenoids and diterpenoids have been identified as the characteristic components.

### Triterpenoids

Triterpenoids are the major chemical compounds present in *R. chingii*. They are mainly pentacyclic triterpenoids or thereof derivatives, with oleane-type and ursane-type skeletons (Figure 1). The first study of triterpenes identified in *R. chingii* dates back to the 1980s, when Masao et al. reported the isolation of a new diosphenol-type triterpene named fupenzic acid (1) (Hattori et al., 1988). In another work (Guo, 2005), the fruits of *R. chingii* were extracted with methanol. Further fractionation of the methanol extract led to the isolation of five oleane-type triterpene acids [oleanic acid (2), maslinic acid (3), arjunic acid (4), 2α, 3α, 19α-trihydroxyolean-12-en-28-oic-acid (5), and sericic acid (6)] together with four ursane-type triterpene acids [ursolic acid (7), 2α-hydroxyursolic acid (8), euscaphic acid (9), and hystaptic acid (10)]. Moreover, Cheng et al. found that the roots of this plant were rich in triterpenoids. They obtained three triterpenes acids, namely, ursolic acid (7), euscaphic acid (9), and hystaptic acid (10). From the 80% ethanol extract of the dried fruits of *R. chingii* yielded nigaichigoside F1 (14) and 2α, 19α-dihydroxy-3-oxo-12-ursen-28-oic acid (15) (Xiao et al., 2011).

### Diterpenoids

Diterpenoids are also characterized as the representative ingredients of *R. chingii*. Currently, 15 diterpenoids (Figure 2), including 2 kaurane-type diterpenoids and 13 labdane-type diterpenoids, have been identified in *R. chingii*. Rubusoside (16) was the first diterpenoid isolated from the methanol extract of the leaves of *R. chingii* in 1981 (Tanaka et al., 1981), and subsequent investigations have led to the isolation of five additional labdane-type diterpene glucosides (Goshonoside-F1-F5, 17–21) (Tanaka et al., 1984). Furthermore, another two labdane-type diterpene glucosides, namely, goshonoside-F6 (22) and goshonoside-F7 (23), were reported to be obtained from both the leaves and fruits of *R. chingii* (Wang, 1991). In 2013, a new ent-labdane diterpene saponin, named goshonoside-G (24), was separated from the 70% ethanol extract of *R. chingii* unripe fruit, and its structure was determined based on NMR spectroscopic studies and mass spectrometry data (Sun et al., 2013b). Later, from the ethyl acetate extract of *R. chingii* fruit, Guo (2015) isolated five labdane-type diterpene glycosides that were elucidated as ent-Labda-8(17),13E-diene-3β, 15,18-triol (25), ent-Labda-8(17),13E-diene-3α, 15,18-triol (26), 15,18-di-O-β-D-glucopyranosyl-13(E)-ent-labda-7(8), 13(14)-diene-3β, 15,18-triol (27), 15,18-di-O-β-D-glucopyranosyl-13(E)-ent-labda-8(9), 13(14)-diene-3β, 15,18-triol (28), and 15-O-β-D-apiofuranosyl-(1→2)β-D-glucopyranosyl-18-O-β-D-glucopyranosyl-13(E)-ent-labda-8(9), 13(14)-diene-3β, 15,18-triol (29). More recently, Zhang et al. (2017b) found a kaurane-type diterpenoid called ent-16α, 17-dihydroxy-kauran-19-oic acid (30) from fruits of *R. chingii* by bio-guided isolation.

### Flavonoids

Flavonoids, occurring naturally in dietary and medicinal plants (Azietaku et al., 2017), are important polyphenol constituents with various pharmacological effects (Cai et al., 2018). The main types of flavonoids found in *R. chingii* were kaempferol, quercetin, and their derivatives. To date, a total of 18 flavonoids have been reported mainly from the fruits of *R. chingii*. Guo et al. isolated six compounds: kaempferol (31), quercetin (32), tiloroside (33), astragaloside (34), quercetin-3-O-β-D-glucopyranosyl (35), and kaempferol-3-O-β-D-glucuronic acid methyl ester (36) (Guo, 2005). In the same year, Liu (2005) obtained kaempferol-7-O-a-L-rhamnoside (37) and 2’-O-Galloyl-hyperin (38). Then, by using a series of chromatographic and spectrum technologies, Cheng (2008) isolated and identified aromadedrin (39), quercitrin (40), hyperoside (41), and cis-tiloroside (42) in 2008. Furthermore, investigation of the 80% ethanol extract of the dried fruits of *R. chingii* yielded phlorizin (43) (Xiao et al., 2011). Lately, kaempferol-3-O-hexoside (44), quercetin-3-O-glucuronide (45), and kaempferol-3-O-glucuronide (46) were identified in the fruits of *R. chingii* by high-performance liquid chromatography (HPLC) coupled with linear ion trap-OrbiTrap hybrid mass spectrometer (Li et al., 2018). In addition, kaempferol-3-O-β-D-rutinoside (47) (He et al., 2013) and rutin (48) (Zhang et al., 2017a) were also found in this plant. Their structures are shown in Figure 3.

### Alkaloids

Alkaloids represent a relatively small class of compounds in *R. chingii*. Only seven of this class of compounds have been isolated from *R. chingii* (Figure 4), with skeletons of the quinoline, isoquinoline, and indole types. In 2008, Chai (2008) reported that from the 95% and 50% ethanol extract of the fruits of *R. chingii*, three alkaloids were isolated and identified as 4-hydroxy-2-oxo-1,2,3,4-terahydroquinoline-4-carboxylic acid (49), methyl 1-oxo-1,2,3,4-terahydroquinoline-4-carboxylic acid (49), methyl 1-oxo-
### TABLE 1 | Chemical constituents of *R. chingii*.

| No. | Chemical component | Part       | Molecular formula | References                          |
|-----|--------------------|------------|-------------------|-------------------------------------|
| 1   | Fupenzic acid      | Fruit      | C_{60}H_{76}O_{32} | Hattori et al., 1988               |
| 2   | Oleic acid         | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 3   | Maslinic acid      | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 4   | Arjunic acid       | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 5   | 2x, 3x, 19α-trihydroxyolean-12-ene-28-oic-acid | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 6   | Seric acid         | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 7   | Ursolic acid       | Fruit, Root| C_{60}H_{76}O_{32} | Guo, 2005; Cheng, 2008             |
| 8   | 2α-hydroxysyringic acid | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 9   | Euscaphic acid     | Fruit, Root| C_{60}H_{76}O_{32} | Guo, 2005; Cheng, 2008             |
| 10  | Hypotactic acid    | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 11  | 11α-hydroxyeuscaphic acid | Root      | C_{60}H_{76}O_{32} | Cheng, 2008                         |
| 12  | 2α,19α,24-trihydroxyurs-12-ene-3-oxo-28-acid | Fruit      | C_{60}H_{76}O_{32} | Chai, 2008                           |
| 13  | Tormentic acid     | Fruit      | C_{60}H_{76}O_{32} | Chai, 2008                           |
| 14  | Nigaihigoside F1   | Fruit      | C_{60}H_{76}O_{32} | Xiao et al., 2011                   |
| 15  | 2α,15α-dihydroxy-3-oxo-12-ursen-28-oic acid | Fruit      | C_{60}H_{76}O_{32} | Xiao et al., 2011                   |
| 16  | Rubusoside         | Leaf       | C_{60}H_{76}O_{32} | Tanaka et al., 1981                 |
| 17  | Goshonoside-F1     | Leaf       | C_{60}H_{76}O_{32} | Tanaka et al., 1981                 |
| 18  | Goshonoside-F2     | Leaf       | C_{60}H_{76}O_{32} | Tanaka et al., 1981                 |
| 19  | Goshonoside-F3     | Leaf       | C_{60}H_{76}O_{32} | Tanaka et al., 1981                 |
| 20  | Goshonoside-F4     | Leaf       | C_{60}H_{76}O_{32} | Tanaka et al., 1981                 |
| 21  | Goshonoside-F5     | Leaf       | C_{60}H_{76}O_{32} | Tanaka et al., 1981                 |
| 22  | Goshonoside-F6     | Leaf, Fruit| C_{60}H_{76}O_{32} | Tanaka et al., 1981                 |
| 23  | Goshonoside-F7     | Leaf, Fruit| C_{60}H_{76}O_{32} | Tanaka et al., 1981                 |
| 24  | Goshonoside-G      | Fruit      | C_{60}H_{76}O_{32} | Wang, 1991                          |
| 25  | ent-Labda-8(17),13E-diene-3β,15,18-triol | Fruit      | C_{60}H_{76}O_{32} | Guo, 2015                           |
| 26  | ent-Labda-8(17),13E-diene-3α,15,18-triol | Fruit      | C_{60}H_{76}O_{32} | Guo, 2015                           |
| 27  | 15,18-Dt-μ-D-glucopyranosyl-13(Ε)-ent-labda-7(8),13(14)-diene-3β,15,18-triol | Fruit      | C_{60}H_{76}O_{32} | Guo, 2015                           |
| 28  | 15,18-Dt-μ-D-glucopyranosyl-13(Ε)-ent-labda-8(9),13(14)-diene-3β,15,18-triol | Fruit      | C_{60}H_{76}O_{32} | Guo, 2015                           |
| 29  | 15-O-μ-D-apiofuranosyl-(1→2)β-D-glucopyranosyl-18-O-μ-D-glucopyranosyl-13(Ε)-ent-labda-8(9),13(14)-diene-3β,15,18-triol | Fruit      | C_{60}H_{76}O_{32} | Guo, 2015                           |
| 30  | ent-16α,17-dihydroxy-kauran-19-oic acid | Fruit      | C_{60}H_{76}O_{32} | Zhang et al., 2017b                 |
| 31  | Kaempferol         | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 32  | Quercetin          | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 33  | Tiliroside         | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 34  | Astragalin         | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 35  | Quercetin-3-0-β-D-glucopyranoside | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 36  | Kaempferol-3-0-β-D-glucuronic acid methyl ester | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 37  | Kaempferol-7-0-α-L-rhamnoside | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 38  | 2*-O-Galloyl-hyperin | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 39  | Aromadendrin       | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 40  | Quercitrin         | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 41  | Hyperoside         | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 42  | cis-Tiliroside     | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 43  | Phlorizin          | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 44  | Kaempferol-3-O-hexoside | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 45  | Quercetin-3-O-glucuronicide | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 46  | Kaempferol-3-glucuronicide | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 47  | Kaempferol-3-O-β-D-rutinoside | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 48  | Rutin              | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 49  | 4-Hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 50  | Methyl 1-oxo-1,2-dihydroquinoline-4-carboxylate | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 51  | 1-oxo-1,2-Dihydroquinoline-4-carboxylic acid | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 52  | Rubusine           | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 53  | Methyl (3-hydroxy-2-oxo-2,3-dihydropyridine-3-y1)-acetate | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 54  | Methylxidinole-3-acetate | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
| 55  | 2-oxo-1,2-Dihydroquinoline-4-carboxylic acid | Fruit      | C_{60}H_{76}O_{32} | Guo, 2005                           |
TABLE 1  | Continued

| No. | Chemical component | Part | Molecular formula | References |
|-----|--------------------|------|-------------------|------------|
| 56  | Vitamin E          | Fruit| C_{20}H_{24}O_{2} | Zhang and Jiang, 2015 |
| 57  | 2,2,4-Trimethyl-pentane | Leaf, Fruit | C_{10}H_{18} | Han et al., 2014; Pi and Wu, 2003 |
| 58  | 2,2,3,3-Tetramethyl-butane | Leaf | C_{10}H_{18} | Han et al., 2014 |
| 59  | 1-Hydroxy-2-methyl-1-phenyl-3-pentanone | Leaf | C_{12}H_{20}O_{2} | Han et al., 2014 |
| 60  | Linalyl acetate    | Leaf, Fruit | C_{12}H_{20}O_{2} | Han et al., 2014; Zhang and Jiang, 2015 |
| 61  | α-Terpinene        | Leaf | C_{10}H_{18} | Han et al., 2014 |
| 62  | α-Thujene          | Leaf | C_{10}H_{18} | Han et al., 2014 |
| 63  | 2-Ethylhexyl acrylate | Leaf | C_{16}H_{20}O_{2} | Han et al., 2014 |
| 64  | trans-Linalool oxide | Leaf, Fruit | C_{10}H_{18}O_{2} | Han et al., 2014; Zhang and Jiang, 2015 |
| 65  | cis-Linalool oxide | Leaf, Fruit | C_{10}H_{18}O_{2} | Han et al., 2014; Zhang and Jiang, 2015 |
| 66  | L-α-Terpineol      | Leaf | C_{10}H_{18}O | Han et al., 2014 |
| 67  | Nerdy acetate      | Leaf | C_{10}H_{18}O_{2} | Han et al., 2014 |
| 68  | cis-p-2-Menthien-1-ol | Leaf | C_{10}H_{18}O | Han et al., 2014 |
| 69  | 2-(2-Butoxyethoxy)-ethanol acetate | Leaf | C_{12}H_{20}O_{2} | Han et al., 2014 |
| 70  | n-Tridecane        | Leaf | C_{16}H_{34} | Han et al., 2014 |
| 71  | 5-Oxohexadecanoate methyl | Leaf | C_{16}H_{34}O_{2} | Han et al., 2014 |
| 72  | 1,4-Hydroxymethylenephenylethane | Leaf | C_{10}H_{18}O_{2} | Han et al., 2014 |
| 73  | Terpineol-4        | Leaf | C_{10}H_{18}O | Han et al., 2014; Zhang and Jiang, 2015 |
| 74  | (E)-1,2,6,6-Trimethyl-1,3-cyclohexadien-1-yl-2-buten-1-one | Leaf | C_{10}H_{18}O | Han et al., 2014 |
| 75  | trans-Caryophyllene | Leaf | C_{10}H_{18} | Han et al., 2014 |
| 76  | Calarene           | Leaf, Fruit | C_{10}H_{18} | Han et al., 2014; Zhang and Jiang, 2015 |
| 77  | Coniferyl alcohol  | Leaf | C_{16}H_{20}O_{2} | Han et al., 2014 |
| 78  | 1-(4,7,7-Trimethyl-3-bicyclo[4.1.0]hept-4-enyl)ethanone | Leaf | C_{16}H_{20}O_{2} | Han et al., 2014 |
| 79  | trans-Dihydrocarvyl acetate | Leaf | C_{16}H_{20}O_{2} | Han et al., 2014 |
| 80  | E-10-Pentadecenol  | Leaf | C_{16}H_{20}O | Han et al., 2014 |
| 81  | Dodecyl aldehyde   | Leaf | C_{16}H_{20}O | Han et al., 2014 |
| 82  | 12-Methytridecane  | Leaf | C_{16}H_{20}O | Han et al., 2014 |
| 83  | 3-Methoxyoctadecic acid-dimethyl ester | Leaf | C_{16}H_{20}O_{4} | Han et al., 2014 |
| 84  | Dibutyl phthalate   | Leaf | C_{16}H_{20}O | Han et al., 2014 |
| 85  | Cedryl formate      | Leaf | C_{16}H_{20} | Han et al., 2014 |
| 86  | Phytol             | Leaf | C_{16}H_{20}O | Han et al., 2014 |
| 87  | 3-Methyl-2-pentanone | Fruit | C_{10}H_{18}O | Pi and Wu, 2003 |
| 88  | 2-Methoxyethyl acetate | Fruit | C_{10}H_{18}O | Pi and Wu, 2003 |
| 89  | 3-Methyl-2-pentane | Fruit | C_{14}H_{18} | Pi and Wu, 2003 |
| 90  | 1,1-Dithioethane   | Fruit | C_{16}H_{20}O | Pi and Wu, 2003 |
| 91  | 2,5-Dimethylfuran | Fruit | C_{10}H_{18}O | Pi and Wu, 2003 |
| 92  | 2-Hexenal          | Fruit | C_{10}H_{18}O | Pi and Wu, 2003 |
| 93  | Xylene             | Fruit | C_{10}H_{18} | Pi and Wu, 2003 |
| 94  | Ethylbenzene       | Fruit | C_{10}H_{18} | Pi and Wu, 2003 |
| 95  | Ethyl formate      | Fruit | C_{10}H_{18}O | Pi and Wu, 2003 |
| 96  | 2-Butanone         | Fruit | C_{10}H_{18}O | Pi and Wu, 2003 |
| 97  | Isovaleraldehyde   | Fruit | C_{10}H_{18}O | Pi and Wu, 2003 |
| 98  | Ethyl acetate      | Fruit | C_{10}H_{18}O | Pi and Wu, 2003 |
| 99  | 2-Methylpentane    | Fruit | C_{10}H_{18} | Pi and Wu, 2003 |
| 100 | 2-Heptanal         | Fruit | C_{10}H_{18}O | Pi and Wu, 2003 |
| 101 | Hexadecanol        | Fruit | C_{10}H_{18} | Pi and Wu, 2003 |
| 102 | 1-Hexene           | Fruit | C_{10}H_{18} | Pi and Wu, 2003 |
| 103 | 1-Methyl-3-isopropylbenzene | Fruit | C_{10}H_{18} | Dian et al., 2005 |
| 104 | 1,2,3,5-Tetramethylbenzene | Fruit | C_{10}H_{18} | Dian et al., 2005 |
| 105 | Durene             | Fruit | C_{10}H_{18} | Dian et al., 2005 |
| 106 | 3-Ethylstyrone     | Fruit | C_{10}H_{18} | Dian et al., 2005 |
| 107 | 2,4-Dimethylstyrone | Fruit | C_{10}H_{18} | Dian et al., 2005 |
| 108 | 2,6-Dimethylcyclohexanol | Fruit | C_{10}H_{18} | Dian et al., 2005 |
| 109 | 1-Hexadecanol      | Fruit | C_{10}H_{18}O | Dian et al., 2005 |
| 110 | Hexahydrofarnesyl acetone | Fruit | C_{10}H_{18}O | Dian et al., 2005 |
| 111 | 3-Hexadecanial     | Fruit | C_{10}H_{18}O | Dian et al., 2005 |
| 112 | 14-Methyl-pentadecanoic acid, methyl ester | Fruit | C_{10}H_{18}O | Dian et al., 2005 |
### TABLE 1 | Continued

| No. | Chemical component | Part | Molecular formula | References |
|-----|--------------------|------|-------------------|------------|
| 113 | Ambrettolide       | Fruit| C_{18}H_{32}O_{2} | Dian et al., 2005 |
| 114 | Nonadecane         | Fruit| C_{17}H_{32}O        | Zhang and Jiang, 2015 |
| 115 | 2-Methylnonadecane | Fruit| C_{20}H_{42}        | Zhang and Jiang, 2015 |
| 116 | Eicosane           | Fruit| C_{20}H_{42}        | Zhang and Jiang, 2015 |
| 117 | α-Pinene           | Fruit| C_{10}H_{16}        | Zhang and Jiang, 2015 |
| 118 | Bicyclo[3.1.0]hexane, 4-methylene-1-\{1-methyl(ethyl)-| Fruit| C_{11}H_{22}O_{2} | Zhang and Jiang, 2015 |
| 119 | Eucalyptol         | Fruit| C_{14}H_{32}O_{2}   | Zhang and Jiang, 2015 |
| 120 | p-Cymene           | Fruit| C_{10}H_{14}        | Zhang and Jiang, 2015 |
| 121 | trans-Sabinene hydrate | Fruit| C_{12}H_{26}O_{2} | Zhang and Jiang, 2015 |
| 122 | y-Terpinene        | Fruit| C_{10}H_{16}        | Zhang and Jiang, 2015 |
| 123 | Linalool           | Fruit| C_{10}H_{20}        | Zhang and Jiang, 2015 |
| 124 | \(\beta\)-trans-Ocimene | Fruit| C_{12}H_{24}O | Zhang and Jiang, 2015 |
| 125 | Methyl thymyl ether | Fruit| C_{11}H_{20}        | Zhang and Jiang, 2015 |
| 126 | \(\beta\)-Elemene  | Fruit| C_{10}H_{18}        | Zhang and Jiang, 2015 |
| 127 | α-Cedrene          | Fruit| C_{10}H_{18}        | Zhang and Jiang, 2015 |
| 128 | 4,7,9-Megastigmatrien-3-one | Fruit| C_{14}H_{20}O_{2} | Zhang and Jiang, 2015 |
| 129 | Tridecanic acid, methyl ester | Fruit| C_{14}H_{30}O_{2} | Zhang and Jiang, 2015 |
| 130 | Linolenyl alcohol  | Fruit| C_{18}H_{30}        | Zhang and Jiang, 2015 |
| 131 | Hexadeconic acid, ethyl ester | Fruit| C_{18}H_{30}O_{2} | Zhang and Jiang, 2015 |
| 132 | 9,12,15-Octadecatrienal | Fruit| C_{20}H_{40}        | Zhang and Jiang, 2015 |
| 133 | 9,12-Octadecadienoic acid, methyl ester | Fruit| C_{18}H_{32}O_{2} | Zhang and Jiang, 2015 |
| 134 | Octadecane, 2-methyl- | Fruit| C_{18}H_{32}O_{2} | Zhang and Jiang, 2015 |
| 135 | (\(\alpha\),12\(\alpha\))-Methyl octadeca-9,12-dienoate | Fruit| C_{18}H_{34}O_{2} | Zhang and Jiang, 2015 |
| 136 | Methyl linolenate  | Fruit| C_{18}H_{34}O_{2} | Zhang and Jiang, 2015 |
| 137 | Linoleic acid ethyl ester | Fruit| C_{18}H_{36}O_{2} | Zhang and Jiang, 2015 |
| 138 | Ethyl linolenate   | Fruit| C_{19}H_{36}O_{2} | Zhang and Jiang, 2015 |
| 139 | (2\(\alpha\))\-3,7,11,15\-Tetramethyl-2-hexadecen-1-ol | Fruit| C_{20}H_{40}O_{2} | Zhang and Jiang, 2015 |
| 140 | 9-Octadecanamide, (\(Z\))- | Fruit| C_{20}H_{32}NO | Zhang and Jiang, 2015 |
| 141 | Tetracosane        | Fruit| C_{24}H_{40}        | Zhang and Jiang, 2015 |
| 142 | Heptacosane        | Fruit| C_{26}H_{42}        | Zhang and Jiang, 2015 |
| 143 | 9,12-Octadecadienoic acid (\(\alpha\),\(\alpha\))-2,3-bis (trimethylsiloxy)propylester | Fruit| C_{30}H_{58}O_{4} | Zhang and Jiang, 2015 |
| 144 | Octacosane         | Fruit| C_{28}H_{48}        | Zhang and Jiang, 2015 |
| 145 | Supraene           | Fruit| C_{20}H_{40}        | Zhang and Jiang, 2015 |
| 146 | Nonacosane         | Fruit| C_{30}H_{60}        | Zhang and Jiang, 2015 |
| 147 | \(\alpha\)-Tocopherol | Fruit| C_{32}H_{52}O_{2} | Zhang and Jiang, 2015 |
| 148 | \(\beta\)-Tocopherol | Fruit| C_{32}H_{52}O_{2} | Zhang and Jiang, 2015 |
| 149 | \(\gamma\)-Tocopherol | Fruit| C_{32}H_{52}O_{2} | Zhang and Jiang, 2015 |
| 150 | Di-n-butyl phthalate | Fruit| C_{32}H_{62}O_{4} | Zhang and Jiang, 2015 |

### COUMARINS

| No. | Chemical component | Part | Molecular formula | References |
|-----|--------------------|------|-------------------|------------|
| 151 | Esculetin          | Fruit| C_{16}H_{20}O_{2} | Liu, 2005 |
| 152 | Eschelin          | Fruit| C_{16}H_{20}O_{2} | Liu, 2005 |
| 153 | Imperatorin       | Fruit| C_{16}H_{20}O_{2} | Liu, 2005 |
| 154 | Rubusin A         | Fruit| C_{16}H_{20}O_{2} | Sun et al., 2011 |
| 155 | Rubusin B         | Fruit| C_{18}H_{20}O_{2} | Liang et al., 2015 |

### STEROIDS

| No. | Chemical component | Part | Molecular formula | References |
|-----|--------------------|------|-------------------|------------|
| 156 | \(\beta\)-Sitosterol | Fruit, Root| C_{28}H_{48}O | Guo, 2005; Cheng, 2008 |
| 157 | Daucosterol        | Fruit, Root| C_{28}H_{48}O | Guo, 2005; Cheng, 2008 |
| 158 | Stigmaster-4-en-\(\delta\)-diol | Fruit| C_{28}H_{48}O | Guo, 2005 |
| 159 | Stigmaster-5-en-3-ol,deate | Fruit| C_{28}H_{48}O | You, 2009 |
| 160 | \(\beta\)-Stigmastone | Fruit| C_{28}H_{48}O | Xiao, 2011 |
| 161 | 7α-Hydroxy-\(\beta\)-sitosterol | Fruit| C_{28}H_{48}O | Du et al., 2014 |
| 162 | Sitosterol palmitate | Fruit| C_{28}H_{48}O | Liu et al., 2014 |
| 163 | Campesterol        | Fruit| C_{28}H_{48}O | Zhang and Jiang, 2015 |
| 164 | \(\gamma\)-Sitosterol | Fruit| C_{28}H_{48}O | Zhang and Jiang, 2015 |

### ORGANIC ACIDS

#### Phenolic acids

| No. | Chemical component | Part | Molecular formula | References |
|-----|--------------------|------|-------------------|------------|
| 165 | 4-Hydroxybenzoic acid | Fruit| C_{4}H_{6}O_{2} | Cheng, 2008 |
| 166 | Ellagic acid        | Fruit| C_{14}H_{24}O_{6} | Cheng, 2008 |
| 167 | Ethyl gallate       | Fruit| C_{7}H_{12}O_{2} | Cheng, 2008 |
| 168 | 5-[3-Hydroxymethyl-5-(3-hydroxypropyl)-7-Methoxyl-2,3-dihydro-benzofuran-2-y]l-2-methoxy-phenol | Fruit| C_{30}H_{42}O_{10} | Guo, 2015 |
| 169 | 4-Hydroxy-3-methoxy benzoic acid | Fruit| C_{4}H_{6}O_{2} | You, 2009 |
| 170 | Gallic acid         | Fruit| C_{6}H_{6}O_{2} | Xie et al., 2005 |
| No. | Chemical component | Part | Molecular formula | References |
|-----|--------------------|------|-------------------|------------|
| 171 | Resveratrol         | Fruit| C_{13}H_{22}O_{6} | Lim et al., 2004 |
| 172 | Methyl brevifolin-carboxylate | Fruit| C_{13}H_{22}O_{6} | Xiao et al., 2011 |
| 173 | Liballinol          | Fruit| C_{16}H_{24}O_{10} | You, 2009 |
| 174 | 4-Hydrobenzaldehyde | Fruit| C_{10}H_{14}O_{5} | Liu, 2005 |
| 175 | Vanilla             | Fruit| C_{17}H_{10}O_{6} | You, 2009 |
| 176 | Raspberry ketone    | Fruit| C_{18}H_{16}O_{12} | Zhang, 2014 |
| 177 | Brevifolin carboxylic acid | Fruit| C_{19}H_{16}O_{10} | Chai et al., 2016 |
| 178 | 4-[3-Hydroxymethyl-5-(3-hydroxypropyl)-2,3-dihydrobenzofuran-2-yl]-2-methoxyphenol | Fruit| C_{20}H_{22}O_{14} | Guo, 2015 |
| 179 | p-Coumaric acid     | Fruit| C_{8}H_{6}O_{3} | Li et al., 2018 |
| 180 | Ellagic acid hexuronide | Fruit| C_{18}H_{14}O_{12} | Li et al., 2018 |
| 181 | Salicylic acid      | Fruit| C_{6}H_{5}O_{2} | Du et al., 2014 |
| 182 | 4-{[(2S,3R)-3-(Hydroxymethyl)-5-(3-hydroxypropyl)-7-methoxy-2,3-dihydro-1-benzofuran-2-yl]-2-methoxyphenol} | Fruit| C_{20}H_{22}O_{14} | Chai, 2008 |
| 183 | Ferulic acid        | Fruit| C_{15}H_{16}O_{5} | Liu, 2005 |
| 184 | 4-Hydroxy-3-methoxybenzoic acid | Fruit| C_{18}H_{16}O_{12} | Xie et al., 2005 |
| 185 | Vanillin            | Fruit| C_{8}H_{6}O_{3} | You et al., 2009 |
| 186 | 4-Hydroxyphenylacetic acid | Fruit| C_{18}H_{16}O_{12} | Cheng, 2008 |
| 187 | Hexacosyl p-coumarate | Fruit| C_{20}H_{22}O_{14} | Guo, 2015 |
| **Fatty acids** | | | | |
| 188 | Dotriacontanoic acid | Fruit| C_{20}H_{22}O_{14} | Xie et al., 2005 |
| 189 | Hexadecanoic acid   | Fruit| C_{16}H_{32}O_{2} | Han et al., 2013 |
| 190 | Stearic acid        | Fruit| C_{18}H_{36}O_{2} | Xie et al., 2005 |
| 191 | Caproic acid        | Fruit| C_{4}H_{8}O_{2} | Pi and Wu, 2003 |
| 192 | n-Heptadecanoic acid | Fruit| C_{17}H_{36}O_{2} | Dian et al., 2005 |
| 193 | Linoleic acid       | Fruit| C_{18}H_{32}O_{2} | Zhang and Jiang, 2015 |
| 194 | 2-Hexadecanoic acid | Fruit| C_{18}H_{32}O_{2} | Liu et al., 2014 |
| 195 | Caprylic acid       | Fruit| C_{8}H_{10}O_{2} | Pi and Wu, 2003 |
| 196 | n-Tetracosyl-p-coumarate | Fruit| C_{23}H_{32}O_{2} | Du et al., 2014 |
| 197 | Octadecanoic acid   | Fruit| C_{18}H_{32}O_{2} | Zhang and Jiang, 2015 |
| 198 | 9-Octadecynoic acid | Fruit| C_{19}H_{30}O_{2} | Zhang and Jiang, 2015 |
| 199 | Oleic acid          | Fruit| C_{18}H_{32}O_{2} | Dian et al., 2005 |
| 200 | N-pentadecanoic acid | Fruit| C_{16}H_{30}O_{2} | Dian et al., 2005 |
| 201 | a-Linolenic acid    | Leaf, Fruit| C_{18}H_{28}O_{3} | Zhang and Jiang, 2015 |
| 202 | Tetradecanoic acid  | Leaf| C_{14}H_{28}O_{2} | Han et al., 2014 |
| 203 | Undecanoic acid     | Leaf| C_{11}H_{20}O_{2} | Han et al., 2014 |
| 204 | trans-Traumatic acid | Leaf| C_{15}H_{24}O_{2} | Han et al., 2014 |
| 205 | Dodecanoic acid     | Leaf| C_{12}H_{22}O_{2} | Han et al., 2014 |
| 206 | n-Hexacosylferulate | Fruit| C_{20}H_{32}O_{2} | Du et al., 2014 |
| 207 | 8,11,14-Eicosatrienoic acid | Fruit| C_{20}H_{30}O_{2} | Zhang and Jiang, 2015 |
| **Tannins** | | | | |
| 208 | Casuarinin          | Fruit| C_{16}H_{32}O_{2} | Li et al., 2018 |
| 209 | Casuarinins         | Fruit| C_{16}H_{32}O_{2} | Li et al., 2018 |
| 210 | Casuarinin         | Fruit| C_{16}H_{32}O_{2} | Li et al., 2018 |
| 211 | Pedunculagin        | Fruit| C_{25}H_{32}O_{2} | Li et al., 2018 |
| **Others** | | | | |
| 212 | Oxalic acid         | Fruit| C_{2}H_{4}O_{2} | Sun et al., 2013a |
| 213 | Tartaric acid       | Fruit| C_{4}H_{6}O_{4} | Sun et al., 2013a |
| 214 | Acetic acid         | Leaf| C_{2}H_{4}O_{2} | Han et al., 2014 |
| 215 | Malic acid          | Fruit| C_{4}H_{6}O_{4} | Sun et al., 2013a |
| 216 | Citric acid         | Fruit| C_{4}H_{6}O_{7} | Sun et al., 2013a |
| 217 | 2-Hydroxyquinoline-4-carboxylic acid | Fruit| C_{14}H_{14}O_{5} | Cheng, 2008 |
| 218 | Shikimic acid       | Fruit| C_{6}H_{8}O_{5} | Liu, 2005 |
| 219 | Phthalic acid       | Fruit| C_{8}H_{6}O_{4} | Zhang and Jiang, 2015 |
| 220 | Mono-n-butyl phthalate | Fruit| C_{7}H_{12}O_{4} | Xie et al., 2013b |
| **OTHER COMPOUNDS** | | | | |
| 221 | Di(2-ethylhexyl) phthalate | Fruit| C_{20}H_{42}O_{4} | Cheng, 2008 |
| 222 | Ascorbic acid       | Fruit| C_{6}H_{8}O_{6} | Sun et al., 2013a |
| 223 | Heptadecanoic acid, 14-methyl, methyl ester | Fruit| C_{21}H_{34}O_{2} | Zhang and Jiang, 2015 |
| 224 | 1-Hexacosanol       | Fruit| C_{20}H_{40}O_{2} | You, 2009 |
| 225 | Adenosine           | Fruit| C_{10}H_{10}N_{6}O_{4} | Du et al., 2014 |
| 226 | H-2-indenone,2,4,5,6,7a-hexahydro-3-(1-methylthyl)-7a-methyl | Fruit| C_{16}H_{32}O_{2} | You, 2009 |
| 227 | Butyl dosocanoate   | Fruit| C_{20}H_{20}O_{2} | Guo, 2005 |
| 228 | Uridine             | Fruit| C_{8}H_{20}O_{4} | Kong et al., 2011 |
TABLE 1 | Continued

| No. | Chemical component                  | Part | Molecular formula | References               |
|-----|-------------------------------------|------|-------------------|--------------------------|
| 229 | Methy-β-D-glucopyranoside           | Fruit| C\(_{7}H_{14}O_{6}\) | Xiao et al., 2011        |
| 230 | Pentacosanol                        | Fruit| C\(_{25}H_{52}O\) | Guo, 2005                |
| 231 | Triacontanol                        | Fruit| C\(_{30}H_{62}O\) | Chai, 2008               |
| 232 | Hentriacontane                      | Fruit| C\(_{31}H_{64}O\) | Guo et al., 2007         |
| 233 | Guanosine                           | Fruit| C\(_{10}H_{13}N_{5}O_{5}\) | Kong et al., 2011 |
| 234 | Glucose                             | Fruit| C\(_{6}H_{12}O\) | You, 2009                |
| 235 | 3,7-Dihydroxy-1,5-dinitrogen cyclooctane | Fruit| C\(_{6}H_{14}N_{2}O_{2}\) | Xie et al., 2013b |

FIGURE 1 | Chemical structures of triterpenoids (1–15) isolated from *R. chingii*. 

1. Triacylglycerol
2. Pentacosanol
3. Triacontanol
4. Hentriacontane
5. Guanosine
6. Glucose
7. 3,7-Dihydroxy-1,5-dinitrogen cyclooctane
FIGURE 2 | Chemical structures of diterpenoids (16–30) isolated from R. chingii.
FIGURE 3 | Chemical structures of flavonoids (31–48) isolated from R. chingii.
2-dihydroisoquinoline-4-carboxylate (50), and 1-oxo-1, 2-dihydroisoquinoline-4-carboxylic acid (51). In 2011, guiding with 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity, another four alkaloids, including rubusine (52), methyl (3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)-acetate (53), methyldioxindole-3-acetate (54), and 2-oxo-1,2-dihydroquinoline-4-carboxylic acid (55), were isolated from the ethanol extract of the same plant part (Ding, 2011).

### Volatile Constituents

Volatile compounds (Figure 5) comprise an important part of *R. chingii* (Pi and Wu, 2003; Dian et al., 2005; Han et al., 2014; Zhang and Jiang, 2015). Han et al. (2014) investigated the volatile constituents from the leaves of *R. chingii* by employing head-space gas chromatography–mass spectrometry (GC/MS) and identified 37 constituents, mainly including hexadecanoic acid (44.97%), tetradecanoic acid (10.88%), and acetic acid (4.13%). In another study conducted in 2015, a total of 58 volatile compounds were identified from the unripe fruits of *R. chingii* using GC/MS (Zhang and Jiang, 2015). According to their structures, these volatile compounds could be divided into eight chemical groups: saturated hydrocarbons (9 compounds), unsaturated hydrocarbons (10 compounds), alcohols (9 compounds), carbonyl compounds (2 compounds), esters (11 compounds), organic acids (7 compounds), oxides and epoxides (8 compounds), and others (2 compounds).

### Coumarins

Coumarins are phenolic compounds characterized by a benzene ring attached to a pyrone ring. They have a fragrant smell and exist throughout the plant kingdom (Azietaku et al., 2017). To date, limited studies have been performed to investigate the coumarins in *R. chingii* and only five coumarins have been isolated, including two simple coumarins and three furocoumarins (Figure 6).

Liu (2005) isolated and identified esculetin (151), esculin (152), and imperatorin (153) from the 70% ethanol extract of the fruits of *R. chingii* by various chromatographic methods. You reported the isolation and structure elucidation of a new furocoumarins, 3,5,9-trihydroxy-7,8-dihydrocyclopenta[g]chromene-2,6-dione (154), which they named Fu-Pen-Zi-Su (You, 2009) or rubusin A (Sun et al., 2011), from the n-butanol extract of the fruits of *R. chingii*. Recently, phytochemical analysis of *R. chingii* afforded a new chromone called rubusin B (155), which was confirmed according to the 1D and 2D NMR data and MS data (Liang et al., 2015).

### Steroids

Phytosterols are a class of physiologically active compounds extensively used in cosmetics, foods, and medicines. In *R. chingii*, steroids are relatively rare, and only nine steroidal metabolites have been reported and characterized (Figure 7). In 2005, three steroids, namely, β-sitosterol (156), daucosterol (157), and stigmast-4-ene-(3β,6α)-diol (158) (Guo, 2005), were found to exist in methanol extract of the fruits of *R. chingii*. Moreover, β-sitosterol (156) and daucosterol (157) were isolated from the roots of *R. chingii* by Cheng in 2008 (Cheng, 2008). In further studies, another steroid called stigmasterol-5-en-3-ol, oleate (159) was obtained from the methylene chloride extract of *R. chingii* fruit (You, 2009). Other steroidal compounds that were isolated from this plant were β-stigmasterol (160) (Xiao, 2011), 7α-hydroxy-β-sitosterol (161) (Du et al., 2014), and sitosterol palmitate (162) (Liu et al., 2014). In addition, campesterol (163) and γ-sitosterol (164) were tentatively elucidated by GC/MS (Zhang and Jiang, 2015).

### Organic Acids

Organic acids are a class of carboxyl-group-containing compounds that could be found in numerous plants worldwide. *R. chingii* extracts contain a high percentage of organic acids.
FIGURE 5 | Chemical structures of volatile compounds (56–150) isolated from *R. chingii*.

FIGURE 6 | Chemical structures of coumarins (151–155) isolated from *R. chingii*. 
A total of 56 organic acids, including 23 phenolic acids (165–187), 20 fatty acids (188–207), 4 tannins (208–211), and 9 other compounds (212–220) have been reported mainly from the fruits of *R. chingii* (Pi and Wu, 2003; Lim et al., 2004; Dian et al., 2005; Guo, 2005; Liu, 2005; Xie et al., 2005; Chai, 2008; Cheng, 2008; You, 2009; You et al., 2009; Xiao et al., 2011; Han et al., 2013; Sun et al., 2013a; Xie et al., 2013b; Du et al., 2014; Han et al., 2014; Liu et al., 2014; Zhang, 2014; Guo, 2015; Zhang and Jiang, 2015; Chai et al., 2016; Li et al., 2018). Detailed information of these organic acid compounds is shown in Table 1 (165–220) and Figure 8.

**Other Compounds**

In addition to these compounds mentioned above, a range of other compounds have also been isolated from *R. chingii*. Detailed information of these compounds is shown in Table 1 (221–235) and Figure 9 (Guo, 2005; Guo et al., 2007; Chai, 2008; Cheng, 2008; You, 2009; Kong et al., 2011; Xiao et al., 2011; Sun et al., 2013a; Xie et al., 2013b; Du et al., 2014; Zhang and Jiang, 2015).

**PHARMACOLOGICAL ACTIVITIES OF R. CHINGII**

As a well-known medicinal plant in TCM, the fruits and leaves of *R. chingii* are widely used for the treatment of various diseases. The major pharmacological properties such as anticomplementary, anticancer, antioxidant, antimicrobial, anti-inflammatory, anti-hypotensive, anti-aging, antithrombotic, antidiabetic, neuroprotective, and anti-osteoporosis activities of this herbaceous medicine are summarized in Table 2, and the details will be further discussed below.

**Anticomplementary Activity**

Several studies demonstrated that the extracts of *R. chingii* possess anticomplementary activity. Zhang and Jiang employed a complement fixation test to assess the *in vitro* anticomplementary activity of the essential oils from fruits of *R. chingii* by three different extraction methods [steam distillation extraction (SDE), soxhlet extraction (SE) with ethanol, and SE with ether]. The results showed that the essential oils obtained by SE-ether had the strongest...
FIGURE 8 | Chemical structures of organic acids (165–220) isolated from R. chingii.
The flavonoids and saponins extracted from *R. chingii* also showed noteworthy anticomplementary activities when compared to its polysaccharides and alkaloids. The hemolysis inhibition rates of the flavonoids and saponins were 96.49% and 90.82% (at the concentration of 0.8 mg/ml), respectively, which were even higher than heparin sodium (Zhang et al., 2015a).

**Anticancer Activity**

The antitumor effects of the various extracts of *R. chingii* have been extensively investigated through a large number of in vivo and in vitro experiments. Wang et al. (2011) found that the water extract of *R. chingii* could inhibit the activities of matrix metalloproteinases-13 with an IC<sub>50</sub> value (half maximal inhibitory concentration) of 0.04 μg/ml. The results suggested that this herbal medicine may be used for the treatment of cancer. Another study showed that the water extract of *R. chingii* gave rise to a dose-dependent antiproliferative effect on hepatocellular carcinoma cells with an IC<sub>50</sub> value of 80 μg/ml (Hu, 2014). Anticancer activity was also reported for the essential oils from the unripe fruits of *R. chingii* by in vitro MTT cytotoxicity assay against A549 cell lines. The results showed that the essential oils extracted by SDE exhibited stronger activity than SE-ethanol, which may be due to the extract obtained by SDE, which had a higher content of unsaturated fatty acids (Zhang and Jiang, 2015). An in vitro study showed that polyphenolic composition in the fruits of *R. chingii* could inhibit the proliferation and induce apoptosis of human bladder cancer T24 cells remarkably in a dose-dependent and time-response manner. The IC<sub>50</sub> values were 73.442, 55.294, and 26.686 μg/ml for 12, 24, and 36 h, respectively (Li et al., 2018). In a similar study, Zhang et al. (2015b) evaluated the anticancer activity of the polysaccharides from *R. chingii* via MTT assay and found that inhibitory activities on breast cancer cells’ MCF-7 and liver cancer cells’ Bel-7402 proliferation were also concentration- and time-dependent. From 70% ethanol extract of the fruits of *R. chingii*, Zhong et al. (2015) isolated three new labdane-type diterpene glycosides and in vitro tests of these compounds for anticancer activity showed that compound 29 possessed remarkable cytotoxic activity against A549 (human lung cancer cell line), with an IC<sub>50</sub> value of 1.81 μg/ml (2.32 μM). Furthermore, tiliroside, a representative flavonoid isolated from *R. chingii*, induced the apoptosis of A549 cells in a dose-dependent manner, with an IC<sub>50</sub> value of 113.41 ± 1.89 μg/ml (190.76 ± 3.18 μM) (Zhang et al., 2015a). In 2017, Zhang et al. (2017b) investigated the antiproliferative ingredients in the fruits of *R. chingii* by using bio-assay guided isolation, and found that tormentic acid possessed notable cytotoxicity activities against HepG-2, Bel-7402, A549, and MCF-7 cancer cell lines with the IC<sub>50</sub> values of 40.57, 54.22, 62.36, and 24.23 μg/ml, respectively. All these results described above suggest that *R. chingii* has an exact effect on prevention of cancer. However, a common mechanism about the exact cellular and molecular targets needs to be fully elucidated and the diversity of extracts makes data interpretation difficult.

**Antimicrobial Activity**

Antimicrobial activity, an important effect of *R. chingii*, had been comprehensively studied. A moderate antibacterial activity was evident for the flavonoids from *R. chingii* against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Penicillium with MIC (minimum inhibitory concentration) values of 0.04, 0.08, 0.16, and 0.64 mg/ml, respectively. However, it could not inhibit the growth of Saccharomyces cerevisiae, Rhizopus, and Mucor.

FIGURE 9 | Chemical structures of other compounds (221–235) isolated from *R. chingii*. 
### TABLE 2 | Reported biological activities in vitro and in vivo of R. chingii crude extracts and fractions.

| Extract | Reported activity | References |
|---------|-------------------|------------|
| **ANTICOMPLEMENTARY ACTIVITY** | Essential oils extracted by SE-ether had the best anti-complementary activity; at 0.2 mg/mL, its hemolysis inhibition exceeded 60% (in vitro). | Zhang and Jiang, 2015 |
| Essential oils from fruits | Flavonoids and saponins showed noteworthy anti-complementary activities; at 0.8 mg/mL, their hemolysis inhibition rates were 96.49% and 90.82%, respectively (in vitro). | Zhang et al., 2015a |
| Polysaccharides, flavonoids, saponins, and alkaloids from fruits | | |
| Polyphenolic composition from fruits | Anticancer potentials against human bladder cancer T24 cells. The IC<sub>50</sub> values were 73.442 μg/mL, 55.294 μg/mL, and 26.686 μg/mL for 12, 24 h and 36 h, respectively (in vitro). | Li et al., 2018 |
| Polysaccharides from fruits and leaves | Polysaccharides from leaves showed significant inhibitory activities on breast cancer MCF-7 proliferation; at 2 mg/mL, its inhibition rate were 48.48 ± 0.55% and 66.30 ± 0.61% for 48 h and 72 h, respectively (in vitro). | Zhang et al., 2015b |
| Labdane-type diterpene glycosides from fruits | Compound 29 possessed remarkable cytotoxic activity against human lung cancer cells A549, with an IC<sub>50</sub> value of 1.81 μg/mL (in vitro). | Zhong et al., 2015 |
| Flavonoids and saponins from fruits | Anticancer potentials against human lung cancer cells A549. The inhibition rates were 65% and 62% (200 μg/mL), respectively (in vitro). | Zhang et al., 2015a |
| The ethyl acetate fraction from fruits | Antiproliferative potentials against HepG2-2, Bel-7402, A549, and MCF-7 cancer cell lines (in vitro). | Zhang et al., 2017b |
| **ANTIMICROBIAL ACTIVITY** | Inhibited Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Penicillium with MIC values of 0.04 mg/mL, 0.08 mg/mL, 0.16 mg/mL, and 0.64 mg/mL, respectively (in vitro). | Zhu, 2012 |
| Flavonoids from fruits | In vitro antioxidant activity (DPPH assay) with an IC<sub>50</sub> values of 3.4 and 4.0 μg/mL, respectively. | Han et al., 2016 |
| 70% ethanol extract from fruits | In vitro antioxidant activity (DPPH assay) with IC<sub>50</sub> values of 3.4 and 4.0 μg/mL, respectively. | Han et al., 2016 |
| **ANTIOXIDANT ACTIVITY** | | |
| Glycoprotein from fruits | In vitro antioxidant activity; in vivo promote the activities of CAT, SOD and GSH-PX. | Tian et al., 2010 |
| Aqueous extract from fruits | Protected primary rat hepatocytes against (r-BHP)-induced rat hepatocytes by reversing cell viability loss, lactate dehydrogenase leakage and the associated glutathione depletion and lipid peroxidation (in vitro). | Yau et al., 2002 |
| The ethyl acetate and n-butanol fractions from fruits | Antioxidant activity (DPPH assay) with an IC<sub>50</sub> value of 33.912 μg/mL. | Ding, 2011 |
| Flavonoids from fruits | In vitro antioxidant activity (DPPH assay and ABTS assay). | Zeng, 2015 |
| Polysaccharides from fruits and leaves | In vitro antioxidant activity (DPPH assay). IC<sub>50</sub>: 754.33 μg/mL (F-Ps); 671.39 μg/mL (L-Ps). | Zhang et al., 2015b |
| Polyphenolic composition from fruits | In vitro antioxidant activity (DPPH assay) with an IC<sub>50</sub> value of 33.912 μg/mL. | Li et al., 2018 |
| 95% ethanol extract from fruits | The ethyl acetate fraction and n-butanol fraction showed significant in vitro antioxidant activity (DPPH assay, reducing power assay and ORAC assay). | Zhang et al., 2017b |
| Flavonoids from fruits | The total flavonoids displayed the best in vitro antioxidant effect (DPPH assay, reducing power assay and ORAC assay), which was very close to ascorbic acid. | Zhang et al., 2015a |
| **ANTI-INFLAMMATORY ACTIVITY** | Anti-inflammatory potentials against LPS-stimulated macrophage RAW264.7 cells (in vitro). | Zhang et al., 2015c |
| Ethyl acetate fraction from fruits | Anti-inflammatory potentials against LPS-stimulated murine macrophage RAW264.7 cells by decreasing NO production and increasing the TNF-α, iNOS and IL-6 gene expression (in vitro). | Zhang et al., 2015b |
| Polysaccharides from fruits and leaves | | |
| **ANTITHROMBOTIC ACTIVITY** | Significant antithrombotic activity was observed in in vitro and in vivo tests. | Han et al., 2012 |
| 70% ethanol fraction from leaves | | |
| **NEUROPROTECTIVE ACTIVITY** | Significant improvements in learning and memory were observed, especially in rats receiving the chloroform and ethylacetate fractions (in vivo). | Huang et al., 2013 |
| 80% ethanol extract from fruits | The high dose water extract (24 g/kg) was found to exhibit the best anti-amnesic effects on scopolamine and sodium nitrite (NaNO<sub>2</sub>)-induced amnestic models, while the crude drug showed the best anti-amnesic activity on 40% ethanol-induced amnestic models (in vivo). | Li et al., 2016a |
| Different extracts from fruits | Water extract from fruits | Amelorlated H<sub>2</sub>O<sub>2</sub>-induced damages of bEnd.3 cells (in vitro). | Liu, 2018 |
| **HYPOLIPIDEMIC ACTIVITY** | Water extract from leaves | | |
| **ANTIHYPOTENSIVE ACTIVITY** | Ethanol extract from fruits | | |
| **TABLE 1 | Reported biological activities in vitro and in vivo of R. chingii crude extracts and fractions.**

| Extract | Reported activity | References |
|---------|-------------------|------------|
| Ethyl acetate fraction from fruits | In vitro antioxidant activity; in vivo promote the activities of CAT, SOD and GSH-PX. | Tian et al., 2010 |
| Aqueous extract from fruits | Protected primary rat hepatocytes against (r-BHP)-induced rat hepatocytes by reversing cell viability loss, lactate dehydrogenase leakage and the associated glutathione depletion and lipid peroxidation (in vitro). | Yau et al., 2002 |
| The ethyl acetate and n-butanol fractions from fruits | Antioxidant activity (DPPH assay) with an IC<sub>50</sub> values of 3.4 and 4.0 μg/mL, respectively. | Ding, 2011 |
| Flavonoids from fruits | In vitro antioxidant activity (DPPH assay and ABTS assay). | Zeng, 2015 |
| Polysaccharides from fruits and leaves | In vitro antioxidant activity (DPPH assay). IC<sub>50</sub>: 754.33 μg/mL (F-Ps); 671.39 μg/mL (L-Ps). | Zhang et al., 2015b |
| Polyphenolic composition from fruits | In vitro antioxidant activity (DPPH assay) with an IC<sub>50</sub> value of 33.912 μg/mL. | Li et al., 2018 |
| 95% ethanol extract from fruits | The ethyl acetate fraction and n-butanol fraction showed significant in vitro antioxidant activity (DPPH assay, reducing power assay and ORAC assay). | Zhang et al., 2017b |
| Flavonoids from fruits | The total flavonoids displayed the best in vitro antioxidant effect (DPPH assay, reducing power assay and ORAC assay), which was very close to ascorbic acid. | Zhang et al., 2015a |
| **ANTITHROMBOTIC ACTIVITY** | Significant antithrombotic activity was observed in in vitro and in vivo tests. | Han et al., 2012 |
| 70% ethanol fraction from leaves | | |
| **NEUROPROTECTIVE ACTIVITY** | Significant improvements in learning and memory were observed, especially in rats receiving the chloroform and ethylacetate fractions (in vivo). | Huang et al., 2013 |
| 80% ethanol extract from fruits | The high dose water extract (24 g/kg) was found to exhibit the best anti-amnesic effects on scopolamine and sodium nitrite (NaNO<sub>2</sub>)-induced amnestic models, while the crude drug showed the best anti-amnesic activity on 40% ethanol-induced amnestic models (in vivo). | Li et al., 2016a |
| Different extracts from fruits | Water extract from fruits | Amelorlated H<sub>2</sub>O<sub>2</sub>-induced damages of bEnd.3 cells (in vitro). | Liu, 2018 |
| **HYPOLIPIDEMIC ACTIVITY** | Water extract from leaves | | |
| **ANTIHYPOTENSIVE ACTIVITY** | Ethanol extract from fruits | | |
(Zhu, 2012). In addition, *R. chingii* extract combined with fluconazole displayed synergistic antifungal activity on fluconazole-resistant *Candida albicans* with an MIC<sub>50</sub> (the lowest concentration to inhibit 50% of fungal growth) value of 0.0625–16 μg/ml for fluconazole and 4.88–312.5 μg/ml for the 70% ethanol extract of *R. chingii* (Han et al., 2016).

### Antioxidant Activity

Oxidative stress by free radicals is a significant event in the cell, which is associated with a wide range of human degenerative diseases (Bi et al., 2016). The glycoprotein from *R. chingii* showed significant *in vitro* antioxidant activity via free radical scavenging assay and reducing power assays. An in-depth *in vivo* study revealed that the glycoprotein could significantly increase the activities of catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) in serum, liver, and brain tissues of rats, which also confirmed the strong reducing power of the glycoprotein (Tian et al., 2010). The aqueous extract of *R. chingii* has also been reported to reverse tert-butyl hydroperoxide (t-BHP)-induced oxidative damage in rat hepatocytes by inhibiting lactate dehydrogenase leakage, lipid peroxidation, and the associated glutathione depletion (Yau et al., 2002). Moreover, among nine compounds isolated from the fruits of *R. chingii*, methyl (3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)-acetate, vanillic acid, kaempferol, and tiliroside displayed antioxidative capacity. Their IC<sub>50</sub> values were 45.2, 34.9, 78.5, and 13.7 μM, respectively (ascorbic acid, 131.8 μM) (Ding, 2011). Zeng et al. studied the *in vitro* antioxidant capacities of the total flavonoid contents of *R. chingii* by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid (ABTS) methods. The results showed that the total flavonoid content exhibited a significant correlation with antioxidant activity in the DPPH assay (r² = 0.758, p = 0.004) and the ABTS assay (r² = 0.788, p = 0.002) (Zeng et al., 2015). Zhang et al. (2015b) investigated the antioxidant effects of fruits of *R. chingii* using the DPPH assay, reducing power assay and oxygen radical absorbance capacity (ORAC) assay, and the results revealed that the ethyl acetate fraction and n-butanol fraction were found to be the most potent (Zhang et al., 2017b). The polysaccharides, flavonoids, saponins, and alkaloids extracted from *R. chingii* were also assessed for their antioxidant activity through the same methods. The results indicated that total flavonoids displayed the best antioxidant effect, which was very close to ascorbic acid (Zhang et al., 2015a). From the results mentioned above, we can conclude that the strong antioxidant activity of *R. chingii* might be predominantly related to the presence of the glycoproteins and phenolic compounds, especially flavonoids. Additionally, it is worthy to note that the *in vitro* experiments used to test total antioxidant are not specific and prone to interferences, which may give unreliable results. Therefore, further *in vivo* studies are needed to validate these results.

### Anti-Inflammatory Activity

Sun et al. (2013b) extracted a new compound called goshonoside-G from the fruits of *R. chingii*. This compound possessed notable inhibitory effect on NO production in LPS-stimulated macrophage RAW264.7 cells with an IC<sub>50</sub> value of 54.98 μg/ml. In bio-assay guided fractionation of the ethanol extract of *R. chingii*, which provided the best anti-inflammatory effect, tiliroside, astragalin, hyperoside, quercitrin, and kaempferol 3-rutinoside were isolated. Among the flavonoid glycosides, tiliroside possessed the strongest inhibitory effect on NO production in LPS-stimulated macrophage RAW 264.7 cells with the inhibitory rate of 30.4% at a concentration of 100 μg/ml, which was very close to that of dexamethasone at a concentration of 50 μg/ml. Western blot and RT-PCR showed that the underlying mechanism of the suppression of inflammatory reactions by tiliroside may be due to its modulation of a signaling mitogen-activated protein kinase (MAPK) and pro-inflammatory cytokines activities (Zhang et al., 2015c). In addition, the polysaccharides from leaves and fruits induced a dose-dependent (2–400 μg/ml) inhibition of the nitric oxide (NO) production in murine macrophage RAW 264.7 cells through suppressing the TNF-α, iNOS, and IL-6 gene expression (Zhang et al., 2015b). Therefore, flavonoid glycosides and polysaccharides along with...
goshonoside-G of the plant could be considered as potential anti-inflammatory agents.

**Antithrombotic Activity**

The 70% ethanol fraction from an aqueous extract of *R. chingii* leaves was found to treat thrombosis through inhibiting the aggregation of blood platelets using activity tests carried out in vitro and in vivo. The bio-guided isolation of the extract yielded six compounds (salicylic acid, kaempferol, quercetin, tiliroside, quercetin 3-O-β-D-glucopyranoside, and kaempferol 3-O-β-D-glucopyranoside). Their anticoagulant activities were examined using plasma recalcification time (PRT) test. It is noteworthy that kaempferol, quercetin, and tiliroside obviously delayed PRT in blood at a concentration of 2 mg/ml, while salicylic acid, quercetin 3-O-β-D-glucopyranoside, and kaempferol 3-O-β-D-glucopyranoside demonstrated the weakest effect in the in vitro experiment (Han et al., 2012).

**Neuroprotective Activity**

Huang et al. investigated whether or not *R. chingii* was involved in attenuating learning and memory deficits on a classical model of Kidney Yang Deficiency Syndrome (KDS-Yang) in Alzheimer's disease rats induced by D-galactose combined with hydrocortisone. Morris water maze tests demonstrated significant improvements in learning and memory, especially in rats receiving the chloroform and ethylacetate fractions of *R. chingii* (Huang et al., 2013). The major mechanism may be that *R. chingii* could protect neurons in rat hippocampal CA1 region by increasing choline acetyltransferase (ChAT) activity but decreasing acetylcholinesterase (AChE) activity and Tau protein expression. The possible memory-enhancing effects of different extracts of *R. chingii* on amnesic rats induced by scopolamine, sodium nitrite, and 40% ethanol were also studied by assessing a Morris water maze test. The results showed that the high-dose water extract (24 g/kg) exhibited the best anti-amnesic effects on scopolamine and sodium nitrite (NaNO₂)-induced amnesia models, while the crude drug showed the best anti-amnesic activity on 40% ethanol-induced amnestic models (Li et al., 2016a). Moreover, Liu et al. (2018) demonstrated that the water extract of *R. chingii* could ameliorate H₂O₂-induced damages of brain microvascular endothelial cells (bEnd.3 cells) via regulating the expression of apoptosis-related proteins. In addition, two flavonoids (kaempferol and quercetin) isolated from *R. chingii* were investigated for neuroprotective activity. It was observed that at 80 μmol/L concentration, both compounds significantly inhibited the decrease of cell viability (MTT reduction), prevented membrane damage (LDH release), scavenged ROS formation, and attenuated the decrease of malondialdehyde (MDA) in H₂O₂-induced PC12 cells (Zhao et al., 2018). These abovementioned results of preclinical investigations show that *R. chingii* may be a promising herbal medicine to combat nerve injury.

**Antidiabetic Activity and Hypolipidemic Activity**

Xie et al. reported antihyperglycemic effects of raspberry ketone in the alloxan-induced diabetic rat model, which were beneficial for the treatment of diabetes. The study showed that raspberry ketone reduced the level of the blood glucose, protected the normal physiological function of pancreatic β cells, and stimulated insulin secretion by effectively inhibiting the oxidative stress (Xie et al., 2012). Another study showed that raspberry ketone could significantly promote glucose uptake in HepG2 cells by increasing the IRS-1 protein expression and decreasing SHP-1 mRNA gene expression (Xie et al., 2014).

The hypolipidemic activity of the leaves from *R. chingii* was evaluated in the hyperlipidemia rats induced by a high-fat diet and adults with hyperlipidemia. The results revealed that treatment with raspberry leaves exhibited significant hypolipidemic effect, indicated by reduced level of serum total cholesterol (TC) and triacylglycerols (TGs). Therefore, it suggested that raspberry leaves could be further explored as a therapy for the treatment of hyperlipidemia diseases (Fan et al., 2007).

**Anti-Osteoporotic Activity**

Liang et al. (2015) isolated a novel compound, rubusin B, and six known compounds from the fruits of *R. chingii*, and an in vitro study showed that rubusin B, kaempferol, rubusin A, and quercetin exhibited anti-osteoporotic activities with different characteristics. Quercetin and kaempferol had a direct stimulatory effect on alkaline phosphatase (ALP) activity and bone formation, while rubusin A and B could effectively attenuate osteoclastic resorption even at a very low concentration (0.01 ppm).

**Antihypotensive Activity**

Recently, it was shown that the ethanol extract of *R. chingii* could induce the endothelium-dependent vasodilatory effect in rats, via stimulation of the NO/guanylate cyclase/cGMP pathway and the Akt-eNOS pathway (Su et al., 2014).

**Anti-Aging Activity**

A novel glycoprotein isolated from *R. chingii* exhibited notable anti-aging effect in the D-galactose-induced aging mouse model by increasing the expression of anti-aging gene klotho and repairing the renal function (Zeng et al., 2018).

**Other Pharmacological Effects**

In addition to the bio-activities mentioned above, some other pharmacological effects of *R. chingii* and its constituents were also reported. Chen et al. (1995) demonstrated that *R. chingii* has mitogenic effects on spleen lymphocytes. They also found that *R. chingii* could regulate the hypothalamus–pituitary–sex gland axis (Chen et al., 1996). Li (2017) reported that *R. chingii* could protect retinal ganglion cells from H₂O₂-induced cell death by increasing the Bcl-2 protein expression and decreasing Bax protein expression.
TOXICITY

Limited data are available concerning the safety assessments of *R. chingii*. In an acute toxicity test, the dose of the water extract of *R. chingii* leaves used in mice was 20 g/kg/day, and it did not induce any toxicity sign or death in 2 weeks (Tang et al., 2007). The potential adverse effects of *R. chingii* leaves were also determined by a repeated dose oral toxicity study, which was conducted on Wistar rats administered for 90 days at oral dosages of 2.5, 5, and 10 g/kg. The researchers found no significant differences between groups in body weights, food consumption, blood biochemistry, organ weights, gross pathology, and histopathology. Further study indicated that *R. chingii* leaves had no mutagenic or genotoxic effect using the Ames test, bone marrow micronucleus test, and sperm aberration test (Tang et al., 2007). Based on the results described above, we can conclude that *R. chingii* leaves are not toxic and hence reliably safe for use for pharmacological purposes. However, more in-depth investigations are still needed to explore the toxicity of the fruits of *R. chingii* to human health.

QUALITY CONTROL

It is well known that the inherent quality of herb medicine may vary significantly in different geographical conditions and different harvest times (Zhang et al., 2018). In the Chinese Pharmacopoeia (2015), the contents of ellagic acid and kaempferol-3-O-rutinoside in *R. chingii* should not be less than 0.2% and 0.03%, respectively (Chinese Pharmacopoeia Commission, 2015). It is extensively accepted that the multiple components of TCM are responsible for their curative effects by exerting their synergistic effects on multiple targets and levels (Li et al., 2016b). Thus, relying only on the two components for quality control seems insufficient to determine the strengths and weaknesses of *R. chingii*. With the advancement of analytical tools, the multi-component determination has been extensively used for comprehensive quality assessment of *R. chingii*. A total of 21 compounds: tiliroside (Chai et al., 2009), kaempferol (Xie et al., 2015; Ping et al., 2016), gallic acid (Li and Tan, 2008), ellagic acid, quercetin-3-O-β-D-glucopyranoside, kaempferol-3-O-rutinoside, goshonoside-F5 (Han et al., 2013), rutin (Zhang et al., 2017a), hyperoside (Chen et al., 1996), astragalin (Zhong et al., 2014; Ma et al., 2017), quercetin (Cheng et al., 2012), malaminic acid, 2α-hydroxyursolic acid, oleanolic acid (Cao et al., 2017), ursolic acid, arjunolic acid, 2α,3α,19α-trihydroxy-12-olean-28-oic acid, euscaphic acid (Guo et al., 2005), adenosine, brevifolin carboxylic acid, and ethyl gallate (Chai et al., 2016), have been quantified by HPLC or CE by different research groups (Chen et al., 2006). The volatile constituents such as hexadecanoic acid, tetradecanoic acid, and acetic acid were detected by GC/MS (Han et al., 2014; Zhang and Jiang, 2015). In addition, a pharmacokinetic study was carried out to determine quercetin-3-O-β-D-glucopyranoside, kaempferol-3-O-rutinoside, and tiliroside in rat plasma after oral administration of *R. chingii* to rats (Zan et al., 2018). However, there is still no unified method for quality control and fingerprinting of *R. chingii*. The quantitative analysis of *R. chingii* is listed in Table 3.

CONCLUSION AND FUTURE PERSPECTIVES

*R. chingii* is a nutritious plant commonly used as a functional food and medicine in China. It has been applied in clinical practice successfully for centuries to tonify the kidney, control nocturnal emissions, and reduce urination (Han et al., 2012). Although chemical compositions and biological activities of this medical plant are well documented, more conclusive studies are still needed to fill certain specific gaps in *R. chingii* science.

Firstly, and particularly, it is noteworthy that most pharmacological studies on *R. chingii* have only been conducted in animal models, cell models, and other in vitro experiments. Therefore, comprehensive placebo-controlled and double-blind clinical trials should be undertaken in the future to provide remarkable evidence for these positive findings on the efficacy of *R. chingii*. Besides, some of the pharmacological studies were carried out at too high doses that could hardly be translated to clinical practice and more in-depth investigations are needed to standardize the best dosage for these claimed bioactivities of *R. chingii* in ethnomedicine. In addition, the exact mechanisms of many medicinal properties of this herb still remain vague to date; thus, additional studies to better identify the functions and molecular targets seem to be necessary.

Secondly, most pharmacological activities were measured using uncharacterized crude extracts of *R. chingii*, and this makes it hard to reproduce the results of these investigations and elucidate the link between activity and particular compounds. Additionally, most of these phytochemicals were isolated from the fruits, and the chemical composition of other parts of this plant was largely unknown. Therefore, in-depth phytochemical investigations of all parts of *R. chingii* based on bio-guided isolation strategies are still needed, which may lead to the expansion of existing therapeutic potential of this miracle herb.

Thirdly, toxicological studies are important to understand the safety profile of herbal drugs, but data on toxicological aspects of *R. chingii* remain unexplored. The only toxicological study about *R. chingii* was conducted in the leaf extract, which revealed its nontoxic nature. Hence, to ensure a full utilization of the medicinal resource, further relative systematic toxicity and safety evaluation studies were quite considerable and necessary, especially in fruit extract and other effective extracts, to meet the Western standards of evidence-based medicine.

Fourthly, pharmacokinetic studies involving *R. chingii* are very limited and only focus on a few biological active substances present in *R. chingii*, which do not fully reflect the pharmacokinetic properties of this herb medicine. Thus, further
investigations should be carried out to assess the absorption, distribution, metabolism, and excretion of the crude extracts of this plant in vivo. Additionally, metabolic studies of single isolated compounds in R. chingii should be strengthened, which could provide a scientific basis for clarifying the major metabolic route and action mechanism and defining the bio-active components responsible for the curative effects. Meanwhile, the identification of unknown metabolites may contribute to the drug discovery and development process.

Lastly, and importantly, because of the complex composition of TCM, quality control of TCM is a great challenge and has become a key factor to restrict its modernization process. Thus, setting up an effective and standardized quality control method of R. chingii is indispensable and emergent, which is

| TABLE | Quantitative analysis for the quality control of R. chingii. |
|-------|-----------------------------------------------------------|
| **Analytes** | **Method** | **Results** | **References** |
| Tiliroside | HPLC | 0.0700% to 0.0338% (contents). | Chai et al., 2009 |
| Tiliroside, Kaempferol | HPLC | 0.1769–0.5150 mg/g and 6.7–23.9 μg/g, respectively (contents). | Ping et al., 2016 |
| Gallic acid | HPLC | 5.24–104.8 μg/ml (linear range); 97.6% (average recovery). | Li and Tan, 2008 |
| Ellagic acid, Quercetin-3-O-β-D-glucopyranoside, Kaempferol-3-O-rutinoside, Tiliroside, Kaempferol, Goshonoside-F5 | HPLC-UV, HPLC-ELSD | 0.078%–0.315%, 0.001%–0.015%, 0.006%–0.065%, 0.003%–0.046%, 0.001%–0.003%, 0%–0.127%, respectively (contents). | He et al., 2013 |
| Ellagic acid, Rutin, Hyperoside, Quercetin-3-O-β-D-glucopyranoside, Kaempferol-3-O-rutinoside, Tiliroside | HPLC | 0.0610%–0.4333%, 0.0008%–0.0024%, 0.0010%–0.0050%, 0.0011%–0.0077%, 0.0058%–0.0284%, 0.0231%–0.1025%, respectively (contents). | Zhang et al., 2017a |
| Astragalin, Tiliroside, Kaempferol | HPLC | 38.24–91.04, 208.14–488.80, 205.68–1624.06, 22.44–84.72 μg/g, respectively (contents). | Ma et al., 2017 |
| Kaempferol-3-O-rutinoside, Astragalin | HPLC | 0.011–0.080 and 0.005–0.020 mg/g, respectively (contents). | Zhong et al., 2014 |
| Rutin, Tiliroside, Quercetin | UPLC | 0.0097–0.0500, 0.21–0.73, and 0.023–0.061 mg/g, respectively (contents). | Cheng et al., 2012 |
| Maslinic acid, 2α-Hydroxyursolic acid, Oleanic acid | HPLC | 0.032%–0.075%, 0.009%–0.053%, and 0.072%–2.087%, respectively (contents). | Cao et al., 2017 |
| Kaempferol | HPLC | 19.91 to 22.26 μg/g (contents). | Xie et al., 2015 |
| Fingerprint | CE (Capillary electrophoresis) | A total of 15 common peaks were found in the HPLC fingerprints of R. chingii. | Chen et al., 2006 |
| Oleanolic acid, Ursolic acid, Maslinic acid, 2α-Hydroxyursolic acid, Arjunic acid, 2α,3α,19α-Trihydroxy-12-Oleanen-28-oic acid, Euscaphic acid | GC/MS | This method is rapid, precise, and reproducible, and is useful for quantitative analysis of the triterpenes | Guo et al., 2005 |
| Volatile constituents | GC/MS | A total of 37 constituents were identified from the leaves of R. chingii, mainly including hexadecanoic acid (44.97%), tetradecanoic acid (10.88%), and acetic acid (4.13%). | Han et al., 2014 |
| Adenosine, Gallic acid, Brevifolin carboxylic acid, Ethyl gallate, Ellagic acid, Kaempferol-3-O-rutinoside, Astragalin, Tiliroside | UPLC | The contents of the eight components vary significantly in the fruits of R. chingii collected from different habitats. And only two compounds, namely, adenosine and ellagic acid, are determined in the ripe fruits of R. chingii. | Chai et al., 2016 |

Cheng et al., 2012 | Ma et al., 2017 | Zhang et al., 2017a | He et al., 2013 | Xie et al., 2015 | Chen et al., 2006 | Guo et al., 2005 | Han et al., 2014 | Chai et al., 2016 | Zhang and Jiang, 2015
crucial for ensuring the safety and efficacy of this medicinal product. In addition, good plant practice ought to be enforced to fulfill quantity and quality requirements for *R. chingii*.

**AUTHOR CONTRIBUTIONS**

GY and ZL searched the literature, collected the data, and drafted the manuscript. GY and WW contributed to analysis and manuscript preparation. YL and YZ helped check the chemical structures and formula. YS provided comments on the manuscript. All authors read and approved the final manuscript.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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