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•Review•

Rubus chingii Hu: an overview of botany, traditional uses, phytochemistry, and pharmacology

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[ABSTRACT] *Rubus chingii* Hu, a member of the rosaceae family, is extensively distributed in China and Japan. Its unripe fruits (Fupenzi in Chinese) have a long history of use as an herbal tonic in traditional Chinese medicine for treating various diseases commonly associated with kidney deficiency, and they are still in use today. Phytochemical investigations on the fruits and leaves of *R. chingii* indicate the presence of terpenoids, flavonoids, steroids, alkaloids, phenylpropanoids, phenolics, and organic acids. Extracts or active substances from this plant are reported to have various pharmacological properties, including antioxidant, anti-inflammatory, antitumor, antifungal, antithrombotic, antiosteoporotic, hypoglycemic, and central nervous system-regulating effects. This review provides up-to-date information on the botanical characterizations, traditional usages, chemical constituents, pharmacological activities, toxicity, and quality control of *R. chingii*. Possible directions for future research are also briefly proposed. This review aims to supply fundamental data for the further study of *R. chingii* and contribute to the development of its clinical use.

[KEY WORDS] *Rubus chingii* Hu; Botany; Traditional uses; Phytochemistry; Pharmacology; Review
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Introduction

Rubus chingii Hu is a perennial crop that is extensively distributed in the Zhejiang, Jiangsu, Anhui, Jiangxi, Fujian and Guangxi provinces of China (Chinese name: "ZhangYe-Fupenzi ") and also in Japan (Japanese name: "Gosho-Ichigo") [1]. Its unripe fruits have been used as a herbal tonic for more than 1500 years in traditional Chinese medicine (TCM) to treat various conditions diseases commonly associated with kidney deficiency, including frequent urination, impotence, and spermatorrhea, and these fruits are still in use today. The leaves of *R. chingii* can be used to treat certain eye diseases, such as eye pain, red eyes, and glaucoma.

Despite the rapid development and outstanding progress in the phytochemical and pharmacological investigations of *R. chingii* in recent years, research on *R. chingii* is still in the initial stages. A systematic review is necessary to advance research on *R. chingii*. In this paper, according to the 120 relevant articles, first, we describe the botanical characterizations of *R. chingii* and its traditional uses. Second, we summarize recent advances in the understanding of the chemical constituents and pharmacology of *R. chingii*. Then, the safety evaluation of this plant and the study of its quality standard are performed and discussed. Finally, we provide suggestions for future studies on *R. chingii*. To the best of our knowledge, to date, no review has covered these aspects of *R. chingii*, and this review will help researchers better understand *R. chingii* and its properties, thereby providing a valuable foundation for further research and development of *R. chingii*.

Materials and Methods

The literature on *R. chingii* was systematically reviewed using the numerous available resources, including classic books regarding Chinese herbal medicine, doctoral dissertations and master's theses, patents, and articles collected from the China Knowledge Resource Integrated datebase, Web of Science, Elsevier, ScienceDirect, PubMed, Scopus, and SciFinder databases. The key words "*Rubus chingii* Hu", "*Rubus chingii*", "traditional uses", "phytochemistry", "pharmacology", "toxicity" and "quality control" were used individu-

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ally or in combination with search literature sources.

Botany

R. chingii, a member of the rosaceae family, grows as a vine shrub and primarily thrives in moist and nonwater-logged soil that is loose and rich in humus. Its roots are distributed mainly in the upper soil. Wild *R. chingii* is usually found in the forest edge, the open forest, hillsides, roadsides, and bushes, where the soil is soft and moist. This plant is approximately 1.5–3 m in height, consists of twigs with prickles, and is hairless (Fig. 1a). *R. chingii* leaves are simple. The leaf blade has a deep cleft and is approximately circular with a diameter of 4–9 cm; its base is heart-shaped, its edge is palmate, lobate oval, or obovate-lozenge; its apex is acuminate; and its base is attenuated to rounded (Fig. 1b). The petiole has a size of 2–4 cm, is glabrous or only puberulent, and has sparse prickles. The flowers are axillary, solitary, and have a diameter of 2.5–4 cm. The pedicles are 2–4 cm in size and hairless. The calyx tubes have sparse hair or are nearly hairless. The sepals are oval or oval-oblong, the apex is abruptly mucronate, and the outside is mixed closely with short fluff. The petals of *R. chingii* are oval or oval-oblong. Their color is white, the apex is obtuse, length is 1–1.5 cm, and width is 0.7–1 cm. The flowering period is from March to April, and the fruiting period is from May to June [1].

The medicinal unripe fruits of *R. chingii* are harvested in early summer, when their color is yellow-green to light brown. These fruits are usually conical or oblate conical, have a height of approximately 0.6–1.3 cm and a diameter of 0.5–1.2 cm, and have an obtuse apex with a concave basal central part (Fig. 1c). The fruit type of *R. chingii* is aggregate and made by achenes. The small fruit grain is easily exfoliated (Fig. 1d). Each fruit is shaped as a half-moon and is densely covered with grayish fuzz [1].

Traditional Uses

The first documented medicinal usage of *R. chingii* was in an ancient Chinese medicinal book titled "*Ming Yi Bie Lu*" (Wei Dynasty, A.D. 220–450, written by Hongjing Tao). According to the book, the unripe fruits of *R. chingii* can invigorate Qi, reduce weight, and blacken hair. Unripe fruits and leaves have been described in many Chinese medical books from the ancient times to the modern age. Additional details on the historical sources and traditional uses of *R. chingii* are listed in Table 1.

It is noticeable that, an old Chinese medicine book titled "*Shen Nong Ben Cao Jing*" (Eastern Han Dynasty, A.D. 25–220) recorded a type of herbaceous plant that is named "Penglei" in Chinese and has an additional name "Fupen". From the standpoint of this book, Penglei and Fupen are the same species. Three older Chinese medical books, namely "*Ben Cao Jing Ji Zhu*" (Northern and Southern Dynasties, A.D. 420–589, written by TAO Hong-Jing), "*Xin Xiu Ben Cao*" (Tang Dynasty, A.D. 618–907, published in A.D. 659) and "*Da Guan Ben Cao*" (Northern Song Dynasty, A.D. 960–1127, published in A.D. 1108), have the same standpoint on this plant. Until A.D. 1116, Penglei and Fupen were distinguished according to the Chinese medical book "*Ben Cao Yan Yi*" (Northern Song Dynasty, A.D. 960–1127, published in A.D. 1116) written by Zongshi Kou. The view that Penglei and Fupen are two different herbaceous plants was further supported by the "*Compendium of Materia Medica*" (Ming Dynasty, A.D. 1368–1644, written in A.D. 1552–1578), written by the great pharmacologist LI Shi-

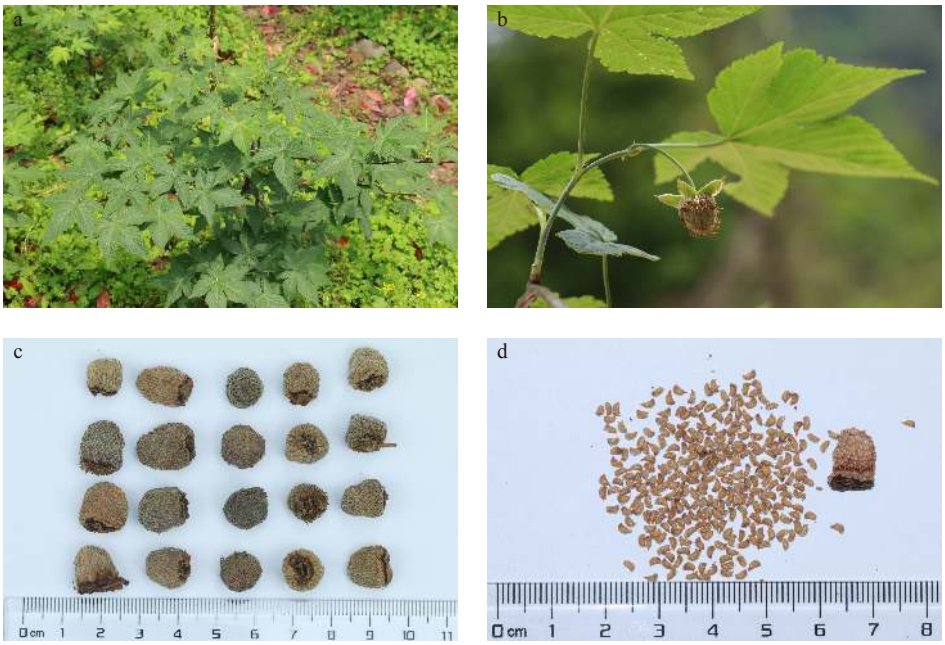


Fig. 1 The entire *R. chingii* plant (a), the fruits and leaves of *R. chingii* (b), the dried unripe fruits of *R. chingii* (c), and the achenes of *R. chingii* (d)

Table 1 Historical sources and the uses of *Rubus chingii* Hu

Historical sources	Traditional uses	Time
Ming Yi Bie Lu [5]	Fruits: Invigorating Qi, losing weight, blackening hair	Wei Dynasty, A.D. 220–450, the precise data is unknown
Yao Xing Lun [6]	Fruits: Tonifying kidney, enriching essence, elevating pregnancy rate for women	Tang Dynasty, A.D. 618–907, the precise data is unknown
Qian Jin Yi Fang [7]	Fruits: Invigorating Qi, losing weight, blackening hair	Tang Dynasty, published in A.D. 682
Kai Bao Ben Cao [8]	Fruits: Tonifying deficiency, restoring luster to the skin, nourishing viscera, warming middle-Jiao, tonifying liver, improving eyesight	Northern Song Dynasty, A.D. 960–1127, written in A.D. 973-974
Jing Shi Zheng Lei Bei Ji Ben Cao [9]	Fruits: Invigorating Qi, losing weight, blackening hair, tonifying kidney, enriching essence, elevating pregnancy rate for women	Northern Song Dynasty, written in A.D. 1097–1108
Ben Cao Yan Yi [10]	Fruits: Tonifying kidney, reducing urine, treating lung-deficiency-related cold	Northern Song Dynasty, published in A.D. 1116
Ben Cao Meng Quan [11]	Fruits: Invigorating Qi, warming middle-Jiao and tonifying deficiency, restoring luster to the skin, improving eyesight, blackening hair	Ming Dynasty, A.D. 1368–1644, published in A.D. 1565
Compendium of Materia Medica [12]	Fruits: Tonifying kidney, treating erectile dysfunction, reducing urine, improving eyesightLeaves: Improving eyesight, removing moisture	Ming Dynasty, written in A.D. 1552–1578
Ben Cao Fa Ming [13]	Fruits: Tonifying kidney, invigorating Qi, warming middle-Jiao, tonifying kidney, preventing spermatorrhea, treating impotence, nourishing viscera, tonifying liver, improving eyesight, blackening hair, losing weight	Ming Dynasty, published in A.D. 1578
Ben Cao Zhen Quan [14]	Fruits: Tonifying deficiency, enriching essence, blackening hair, elevating pregnancy rate for womenLeaves: Treating red eye pain	Ming Dynasty, published in A.D. 1602
Lei Gong Pao Zhi Yao Xing Jie [15]	Fruits: Tonifying kidney, preventing spermatorrhea, treating impotence, reducing urine, improving eyesight, blackening hair, elevating pregnancy rate for women	Ming Dynasty, published in A.D. 1619
Shen Nong Ben Cao Jing Shu [16]	Fruits: Invigorating Qi, enriching essence, losing weight, blackening hair, nourishing viscera	Ming Dynasty, published in A.D. 1625
Ben Cao Xin Bian [17]	Fruits: Invigorating Qi, warming middle-Jiao, tonifying kidney, preventing spermatorrhea, losing weight	Qing Dynasty, A.D. 1636–1912, the precise data is unknown
Ben Cao Qiu Yuan [18]	Fruits: Tonifying liver and kidney, preventing spermatorrhea, improving eyesight, treating impotence, reducing urine, nourishing viscera, blackening hairLeaves: Treating red eye pain	Qing Dynasty, the precise data is unknown
Ben Cao Yue Yan [19]	Fruits: Tonifying kidney, enriching essence, treating impotence	Qing Dynasty, published in A.D. 1660
Ben Cao Tong Xuan [20]	Fruits: Preventing spermatorrhea, treating impotence, reducing urine	Qing Dynasty, published in A.D. 1667
Ben Cao Chong Yuan [21]	Fruits: Nourishing viscera, enriching essence, invigorating Yin, tonifying kidney	Qing Dynasty, written in A.D. 1674–1767
Ben Cao Bei Yao [22]	Fruits: Tonifying liver and kidney, preventing spermatorrhea, improving eyesight, reducing urine, treating impotence, restoring luster to the skin, blackening hair, elevating pregnancy rate for womenLeaves: Treating red eye pain	Qing Dynasty, published in A.D. 1694
Ben Cao Feng Yuan [23]	Fruits: Nourishing viscera, enriching essence, invigorating Yin, losing weight	Qing Dynasty, published in A.D. 1695
Ben Cao Cong Xin [24]	Fruits: Tonifying liver and kidney, preventing spermatorrhea, improving eyesight, treating lung-deficiency-related cold, blackening hairLeaves: Relieving sore	Qing Dynasty, published in A.D. 1757
De Pei Ben Cao [25]	Fruits: Tonifying liver and kidney, reducing urine, treating lung-deficiency-related cold, treating impotence, improving eyesightLeaves: Treating glaucoma	Qing Dynasty, published in A.D. 1761
Ben Cao Qiu Zhen [26]	Fruits: Preventing spermatorrhea, restoring luster to the skin, blackening hair, treating impotence, elevating pregnancy rate for women	Qing Dynasty, A.D. 1636–1912, published in A.D. 1769

Continued

Historical sources	Traditional uses	Time
Ben Cao Zheng Yi [27]	Fruits: Tonifying kidney, reducing urine, strengthening bone and musculature, improving eyesight	Qing Dynasty, published in A.D. 1828
Ben Cao Fen Jing [28]	Fruits: Tonifying liver and kidney, preventing spermatorrhea, improving eyesight, reducing urine, treating impotenceLeaves: Treating red eye pain	Qing Dynasty, published in A.D. 1840
Ben Cao Hui Zuan [29]	Fruits: Tonifying kidney, reducing urine, preventing spermatorrhea, treating impotence, restoring luster to the skin, nourishing viscera, improving eyesightLeaves: Treating red eye pain	Qing Dynasty, published in A.D. 1863
Ben Cao Bian Du [30]	Fruits: Tonifying liver and kidney, preventing spermatorrhea	Qing Dynasty, published in A.D. 1887
Chinese Materia Medica [31]	Fruits: Clearing heat and detoxifying, improving eyesight, healing sore	China A.D. 1949–, published in A.D. 1999
Chinese Pharmacopoeia [32]	Fruits: Tonifying kidney, preventing spermatorrhea, reducing urine	China, published in A.D. 2015

Zhen. According to the "Flora of China", Penglei is *Rubus hirsutus* Thunb. rather than *R. chingii* [1].

Because of its inherent pharmacodynamics effects, unripe fruits of *R. chingii* have been widely used as a key ingredient in some TCM formulations for thousands of years, such as Siwu Wuzi Wan [2], Basheng Dan [3], Michuan Guben Wan [4] and others. Additional details are listed in Table 2. Currently, these prescriptions are still widely used in clinics and are sold in drugstores across China in the form of Chinese Proprietary Medicines. All of these medicines are used to improve or eliminate different types of kidney deficiencies.

Phytochemistry

To date, 105 chemical constituents have been isolated from the fruits and leaves of *R. chingii* and identified (Fig. 2). The main constituents include terpenoids, flavonoids, steroids, alkaloids, phenylpropanoids, phenolics, organic acids, and others. All the compounds of *R. chingii* are summarized in Table 3.

Terpenoids

Terpenoids, including diterpenoids and triterpenoids, are a typical category of compounds present in the genus *Rubus*. In *R. chingii*, diterpenoids and triterpenoids are the characteristic substances. Diterpenoids were proposed to exist only in the leaves and not in the fruits of *R. chingii* [48]. According to our summary, this viewpoint is false. Diterpenoids can exist in both the leaves and fruits of *R. chingii*. 16 kinds of diterpenoids have been isolated and identified from the fruits and leaves of *R. chingii*: 6 ent-labdane-type diterpene glucosides, namely goshonoside F1 (**1**) [49], goshonoside F2 (**2**) [49], goshonoside F3 (**3**) [49], goshonoside F4 (**4**) [49], goshonoside F5 (**5**) [49], and goshonoside F7 (**6**) [50]; 3 pimarene-type diterpenes, namely hythiemoside A (**8**) [50], hythiemoside B (**9**) [50], 14*β*, 16-epoxy-7-pimarene-3*α*, 15*β*-diol (**10**) [50]; 1 kauran-type diterpene, namely sugeroside (**11**) [50]; 1 kaurene-type diterpene, namely rubusoside (**12**) [50]; 4 ent-labdane-type diterpene glycosides, namely goshonoside-G (**7**) [51], 15, 18-Di-*O*-*β*-D-glucopyranosyl-13(*E*)-ent-labda-7(8), 13(14)-diene-3*β*, 15, 18-triol (**14**) [52], 15, 18-triol, 15-*O*-*β*-D-apiofuranosyl-(1→2)-*β*-D-glucopyranosyl-18-*O*-*β*-D-glucopyranosyl-13(*E*)-ent-labda-8(9), 13(14)-diene-3*β*, 15, 18-triol (**15**) [52], and 15,18-Di-*O*-*β*-D-glucopyranosyl-13(*E*)-ent-labda-8(9), 13(14)-diene-3*β*, 15, 18-triol (**16**) [52]; and 1 kauran-type diterpene, namely ent-16*α*, 17-dihydroxy-kauran-19-oic acid d (**13**) [53]. Compounds **1**–**6**, **8**–**12** were isolated from the MeOH extract of dried *R. chingii* leaves [49, 50]. Compounds **7**, **13**–**16** were isolated from the EtOH extract of *R. chingii* fruits [51-53].

15 kinds of triterpenoids, including ursane-type triterpenoids and oleanane-type triterpenoids, have been isolated from the fruits of *R. chingii*. The following ursane-type triterpenoids have been isolated: 2-oxopomolic acid (**17**) [54], 2*α*, 19*α*-dihydroxy-3-oxo-urs-12-en-28-oic acid (**18**) [54], 2*α*-hydroxy-ursolic acid (**19**) [55], ursolic acid (**20**) [55], euscaphic acid (**21**) [55], nigaichigoside F1 (**22**) [56], fupenzic acid (**23**) [57], tormentic acid (**24**) [58], hyptatic acid (**25**) [59], and 2*α*, 19*α*, 24-trihydroxyurs-12-ene-3-oxo-28-acid (**26**) e-3-oxo-28-acid (**26**) [58]. 5 oleanane-type triterpenoids have been isolated from the fruits of *R. chingii*: oleanolic acid (**27**) [55], maslinic acid (**28**) [55], arjunic acid (**29**) [55], 2*α*, 3*α*, 19*α*-trihydroxy-olean-12-ene-28-oic-acid (**30**) [55], and sericic acid (**31**) [59].

Steroids

Almost all higher plants can synthesize steroid compounds, which are one of the broadest spectra of natural products. The steroids in *R. chingii* include daucosterol (**32**) [60], *β*-sitosterol (**33**) [61], stigmast-5-en-3-ol, oleate (**34**) [62], stigmast-4-ene-3*β*, 6*α*-diol (**35**) [59], and 7-Hydroxy-sitosterol (**36**) [63].

Flavonoids

Flavonoids are diffusely distributed in *R. chingii*. 15 flavonoids have been isolated from the fruits and leaves of *R. chingii*. Among them, 10 flavonoids have been isolated from the fruits of *R. chingii*: rutin (**37**) [56], kaempferol-7-*O*-*α*-L-rhamnoside (**38**) [64], hyperoside (**39**) [65], kaempferol-3-*O*-rutinoside (**40**) [65], quercitrin (**41**) [65], phlorizin (**46**) [56], aromadendrin (**47**) [63], 2″-*O*-galloylhyperin (**48**) [64], kaempferol-

Table 2 Prescriptions and its traditional uses of unripe fruits of *Rubus chingii* Hu

Preparation name	Main composition	Traditional use	Origin	Time
Qingyun Powder [33]	Rubi Fructus, Schisandrae, Asparagi Radix, Cuscutae Semen, Taxilli Herba, etc.	Treating impotence	*Qian Jin Yao Fang*	Tang Dynasty, A.D. 618–907, published in A.D. 652
Jixiang Pill [34]	Gastrodiae Rhizoma, Broussone Tiaefructus, Atractylodis Macrocephalae Rhizoma, Cuscutae Semen, Rubi Fructus, etc.	Elevating pregnancy rate for women	*Qian Jin Yao Fang*	Tang Dynasty, published in A.D. 652
Baiwei Pill [34]	Gastrodiae Rhizoma, Broussone Tiaefructus, Atractylodis Macrocephalae Rhizoma, Cuscutae Semen, Rubi Fructus, etc.	Elevating pregnancy rate for women	*Qian Jin Yao Fang*	Tang Dynasty, published in A.D. 652
Fupengzi Powder [35]	Rubi Fructus, Schisandrae Chinensis Fructus, Dendrobii Caulis, Plantaginis Semen, Asparagi Radix, etc.	Tonifying deficiency, enriching essence, strengthening bone and musculature	*Tai Ping Sheng Hui Fang*	Northern Song Dynasty, A.D. 960–1127, written in A.D. 978–992
Shanzhuyu Pill [36]	Corni Fructus, Plantaginis Semen, Atractylodis Macrocephalae Rhizoma, Cibotii Rhizoma, Rubi Fructus, etc.	Warming the kidney and tonifying yang, enriching essence, reducing urine	*Sheng Ji Zong Lu*	Northern Song Dynasty, written in A.D. 1111–1117
Siwu Wuzi Pill [2]	Lycii Fructus, Cuscutae Semen, Rubi Fructus, Schisandrae Chinensis Fructus, Plantaginis Semen, etc.	Tonifying liver and kidney, nourishing the blood	*Pu Ji Fang*	Ming Dynasty, A.D. 1368–1644, published in A.D. 1390
Wuzi Yanzong Pill [37]	Rubi Fructus, Schisandrae Chinensis Fructus, Plantaginis Semen, Cuscutae Semen, Lycii Fructus, etc.	Tonifying kidney, enriching essence	*She Sheng Zhong Miao Fang*	Ming Dynasty, published in A.D. 1550
Michuan Guben Pill [4]	Ginseng Radix Et Rhizoma, Cuscutae Semen, Eucommiae Cortex, Morindae Officinalis Radix, Rubi Fructus, etc	Tonifying deficiency, enriching essence and blood, Nourishing viscera	*Ren Shu Bian Lan*	Ming Dynasty, published in A.D. 1585
Jiawei Caojin Pellet [38]	Morindae Officinalis Radix, Asparagi Radix, Polygalae Radix, Alismatis Rhizoma, Rubi Fructus, etc.	Tonifying deficiency	*Ren Shu Bian Lan*	Ming Dynasty, published in A.D. 1585
Jiawei Liuzi Pill [39]	Morindae Officinalis Radix, Asparagi Radix, Polygalae Radix, Alismatis Rhizoma, Rubi Fructus, etc.	Treating impotence, elevating pregnancy rate for women	*Ren Shu Bian Lan*	Ming Dynasty, published in A.D. 1585
Basheng Pellet [3]	Rubi Fructus, Euryales Semen, Cuscutae Semen, Corni Fructus, Nelumbinis Stamen, etc.	Treating infertility in men and women	*Qi Fang Lei Bian*	Qing Dynasty, A.D. 1636–1912, the precise data is unknown
Quanlu Pill [40]	Cervus, Cynomorii Herba, Codonopsis Radix, Rehmanniae Radix, Rubi Fructus, etc.	Tonifying kidney, enriching essence, Invigorating spleen and Qi	Chinese Pharmacopoeia (2015 version)	China A.D. 1949, published in A.D. 2015
Nankang Tablet [41]	Paeoniae Radix Rubra, Rehmanniae Radix Praeparata, Cistanches Herba, Taraxaci Herba, Rubi Fructus, etc.	Tonifying kidney, detoxicating and activating blood	Chinese Pharmacopoeia (2015 version)	China, published in A.D. 2015
Guilu Bushen Pill [42]	Cuscutae Semen, Cibotii Rhizoma, Ziziphi Spinosae Semen, Polygoni Multiflori Radix, Rubi Fructus, etc.	Tonifying kidney, enriching essence, Invigorating Qi and Yang, strengthening bone and musculature	Chinese Pharmacopoeia (2015 version)	China, published in A.D. 2015
Kunbao Pill [43]	Ligustri Lucidi Fructus, Rubi Fructus, Cuscutae Semen, Lycii Fructus, Polygoni Multiflori Radix Praeparata, etc	Tonifying liver and kidney, nourishing the blood and tranquilization	Chinese Pharmacopoeia (2015 version)	China, published in A.D. 2015
Shenbao Mixture [44]	Cnidii Fructus, Chuanxiong Rhizoma, Cuscutae Semen, Psoraleae Fructus, Rubi Fructus, etc.	Warming the kidney and tonifying yang, enriching essence, invigorating spleen and Qi	Chinese Pharmacopoeia (2015 version)	China, published in A.D. 2015

Continued

Preparation name	Main composition	Traditional use	Origin	Time
Yishenling Granules [45]	Lycii Fructus, Ligustri Lucidi Fructus, Aconiti Lateralis Radix Praeparata, Euryales Semen, Rubi Fructus, etc.	Warming the kidney and tonifying yang,	Chinese Pharmacopoeia (2015 version)	China, published in A.D. 2015
Tiaojing Cuyun Pill [46]	Cervi Cornu Pantotrichum, Epimedii olium, Curculiginis Rhizoma, Dipsaci Radix, Rubi Fructus, etc.	Warming the kidney and invigorating spleen, activating blood and regulating menstruation	Chinese Pharmacopoeia (2015 version)	China, published in A.D. 2015
Qiangyang Baoshen Pill [47]	Epimedii olium, Cnidii Fructus, Cistanches Herba, Poria, Rubi Fructus, etc.	Warming the kidney and tonifying yang	Chinese Pharmacopoeia (2015 version)	China, published in A.D. 2015

3-*O*-*β*-D-glucuronic acid methyl ester (**49**) [66] and cis-tiliroside (**50**) [64]. 2 flavonoids: astragalin (**43**) [65] and tiliroside (**51**) [65] have been isolated from the leaves of *R. chingii*. The other 3 flavonoids, namely kaempferol (**42**) [61], quercetin (**44**) [61], and isoquercitrin (**45**) [67], were isolated from both the fruits and leaves of *R. chingii*.

Alkaloids

The alkaloids that have been isolated from the fruits of *R. chingii* are as follows: 2 indole alkaloids, namely methyldioxindole-3-acetate (**52**) [68] and methyl (3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)-acetate (**53**) [68]; 2 quinoline alkaloids, namely 2-hydroxyquinoline-4-carboxylic acid (**54**) [68] and 4-hydroxy-2-oxo-1, 2, 3, 4-terahydroquino-line-4-carboxylic acid (**55**) [58]; 1 seven-membered ring lactam alkaloid, namely rubusine (**56**) [68]; 2 isoquinoline alkaloids, namely methyl 1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**57**) [58] and 1-oxo-1, 2-dihydroisoquinoline-4-carboxylic acid (**58**) [63].

Phenylpropanoids

9 phenylpropanoids, namely *n*-tetracosyl-p-coumarate (**59**) [63], esculetin (**60**) [64], esculin (**61**) [64], hexacosyl-p-coumarate (**62**) [60], rubusin A (**63**) [61], imperatorin (**64**) [64], rubusin B (**65**) [61], liballinol (**66**) [61], and ferulic acid (**67**) [12] have been isolated from the fruits of *R. chingii*. 5 of them, namely imperatorin, esculetin, esculin, rubusin A, and rubusin B, are also coumarins.

Phenolics

12 phenolics have been isolated from the fruits of *R. chingii*, namely 4-hydroxybenzonic acid (**68**) [66], salicylic acid (**69**) [67], vanillic acid (**70**) [68], vanillin (**71**) [62], 4-hydrobenzal dehyde (**72**) [62], 4-hydroxyphenylacetic acid (**73**) [63], ellagic acid (**74**) [69], methyl brevifolincarboxylate (**75**) [56], shikimic acid (**76**) [70], gallic acid (**77**) [56], ethyl gallate (**78**) [53], and raspberry ketone (**79**) [71].

Organic acids

Organic acids are widely distributed in the leaves, roots, and especially fruits of plants used in Chinese herbal medicines. Moreover, 2*α*-hydroxyursolic acid, ursolic acid, euscaphic acid, fupenzic acid, tormentic acid, 2*α*, 19*α*-dihydroxy-3-oxo-urs-12-en-28-oic acid, hyptatic acid B, 2*α*, 19*α*, 24-trihydroxyurs-12-ene-3-oxo-28-acid, oleanolic acid, maslinic acid, arjunic acid, sericic acid, 2*α*, 3*α*, 19*α*-trihydroxyolean-12-ene-28-oic-acid, 2-hydroxyquinoline-4-carboxylic acid, 4-hydroxy-2-oxo-1, 2, 3, 4-terahydroquinoline-4-carboxylic acid, 4-hydroxybenzonic acid, hydroxy methoxy benzoic acid, gallic acids, salicylic acid, vanillic acid, ferulic acid, shikimic acid, and 4-hydroxyphenylacetic acid exist in the forms of triterpenes, alkaloids, and phenolics. Furthermore, 10 aliphatic carboxylic acids have been obtained and identified from the fruits of *R. chingii*, namely gaidic acid (**80**) [72], oleic acid (**81**) [72], hexanoic acid (**82**) [72], dodecanoic acid (**83**) [72], myristic acid (**84**) [72], pentadecanoic acid (**85**) [72], hexadecanoic acid (**86**) [73], heptadecanoic acid (**87**) [72], stearic acid (**88**) [60, 72] and lacceroic acid (**89**) [60].

Other components

Other components in *R. chingii* include essential oils, amino acids, metallic elements, and polysaccharides. 15 kinds of essential oils have been found, namely 2,6-dimethylcyclohexanol (**90**) [72], *α*-terpineol (**91**) [72], m-cymene (**92**) [72], benzene(**93**) [72], durene (**94**) [72], 1-ethenyl-2,4-dimethylbenzene (**95**) [72], 1-hexadecanol (**96**) [72], nonadecane (**97**) [72], eicosane (**98**) [72], hexadecanal (**99**) [72], 14-methyl-pentadecanoic acid, methyl ester (**100**) [72], *β*-sitosterol gaidic acid ester (**101**) [74], oxacycloheptadec-7-en-2-one (**102**) [72], diisobutyl phthalate (**103**) [72], 1H-2-indenone, 2, 4, 5, 6, 7, 7*α*-hexahydro-3-(1-methylethyl)-7*α*-methyl (**104**) [62] and dibutyl phthalate (**105**) [72]. In addition, *R. chingii* contains polysaccharides; several amino acids, such as threonine, valine, methionine, leucine, phenylalanine, lysine, and aspartic acid [75] and metallic elements, including Zn, Na, Mg, Fe, and Mn [50].

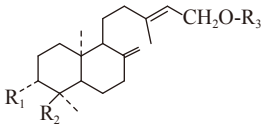
Pharmacology

The pharmacological studies of *R. chingii* have reported that this plant exhibits antioxidant, anti-inflammatory, antitumor, antifungal, antithrombotic, antiosteoporotic, hypoglycemic, and central nervous system-regulating effects.

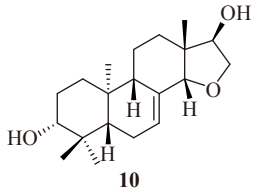
Antioxidant activity

It is widely acknowledged that oxidative damage plays an important role in the pathogenesis of various functional disorders and diseases, including inflammation, aging and neurodegeneration [76-79]. Because of the potential health hazards of synthetic antioxidants, the emphasis of the research is to identify more effective and low-toxicity natural antioxidants from natural medicines. Antioxidant activities of *R. chingii* have been studied *in vivo* and *in vitro*.

One study evaluated the protective action of an aqueous extract of *R. chingii* fruits against tert-butyl hydroperoxide (t-BHP)-induced oxidative stress in rat hepatocytes (50–200 $\mu g \cdot mL^{-1}$ for 24 h). Results indicated that *R. chingii* fruit extract could reverse the decrease of the t-BHP-induced cell survival rate, the increase of lactate dehydrogenase release, and associated lipid peroxidation and glutathione depletion. Pretreatment of *R. chingii* fruit extract also reduced the



	R_1	R_2	R_3
1	OH	CH_2OH	Glc
2	OH	CH_2O-Glc	H
3	H	COO-Glc	Glc
4	H	CH_2O-Glc	Glc
5	OH	CH_2O-Glc	Glc
6	*O*-Glc	CH_3	Glc
7	OH	CH_2O-Glc (6→1) Ara	Glc



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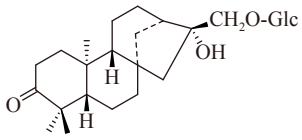

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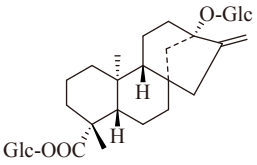

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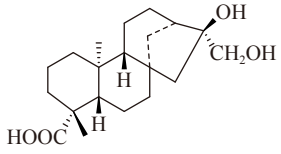

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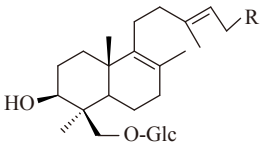
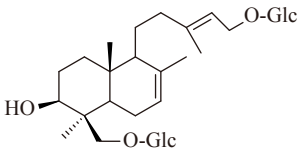


14 R = *O*-Glc
15 R = *O*-Glc (3→1) Apiose



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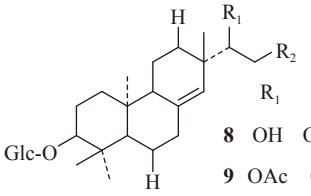
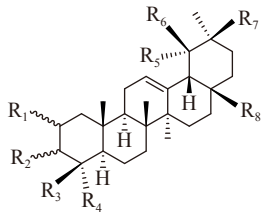
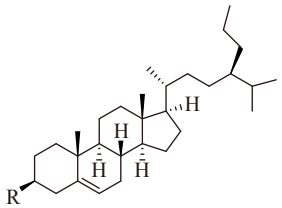


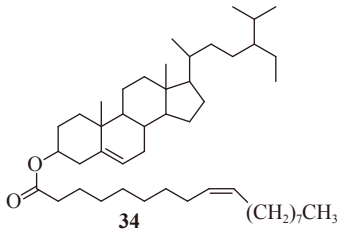
	R_1	R_2
8	OH	OAc
9	OAc	OH



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
17	=O	*α*-OH	CH_3	CH_3	OH	CH_3	H	COOH
18	*α*-OH	=O	CH_3	CH_3	OH	CH_3	H	COOH
19	*α*-OH	*β*-OH	CH_3	CH_3	H	CH_3	H	COOH
20	H	*β*-OH	CH_3	CH_3	H	CH_3	H	COOH
21	*α*-OH	*α*-OH	CH_3	CH_3	CH_3	CH_3	H	COOH
22	*α*-OH	*β*-OH	CH_3CH_2OH		OH	CH_3	H	COO-Glc
23	*α*-OH	=O	CH_3	CH_3	OH	CH_3	H	COOH
24	*α*-OH	*β*-OH	CH_3	CH_3	OH	CH_3	H	COOH
25	*α*-OH	*β*-OH	CH_2OH	CH_3	CH_3	CH_3	H	COOH
26	*α*-OH	=O	CH_3	CH_2OH	OH	CH_3	H	COOH
27	H	*β*-OH	CH_3	CH_3	H	H	CH_3	COOH
28	*α*-OH	*β*-OH	CH_3	CH_3	H	H	CH_3	COOH
29	*α*-OH	*β*-OH	CH_3	CH_3	H	H	CH_3	COOH
30	*α*-OH	*α*-OH	CH_3	CH_3	OH	H	CH_3	COOH
31	*α*-OH	*β*-OH	CH_2OH	CH_3	OH	H	CH_3	COOH



32 R = OH
33 R = O-Glc



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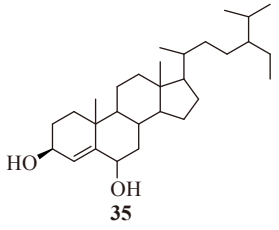

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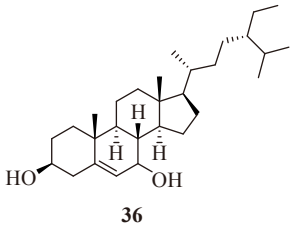

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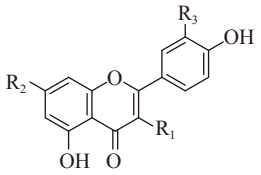

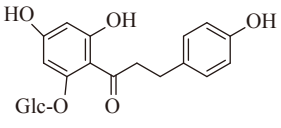

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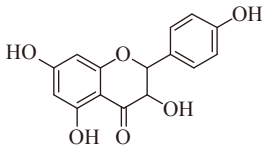
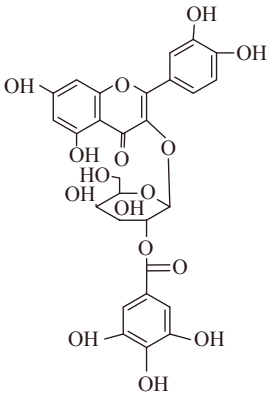


47

	R_1	R_2	R_3
37	O-Glc (6→1) Rha	OH	OH
38	OH	O-Rha	
39	O-Gal	OH	OH
40	O-Glc (6→1) Rha	OH	H
41	O-Rha	OH	OH
42	OH	OH	H
43	O-Gal	OH	H
44	OH	OH	OH
45	O-Gal	OH	OH



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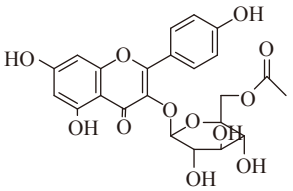

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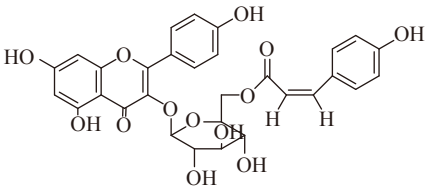

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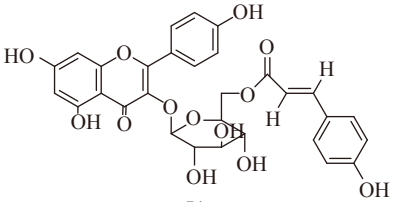

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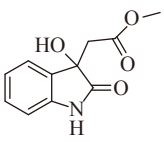

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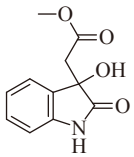

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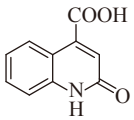

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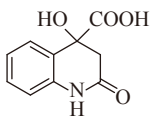

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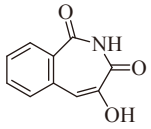

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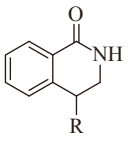
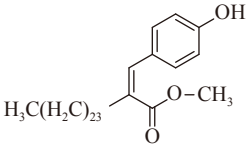


57 R = $COOCH_3$

58 R = COOH



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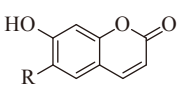
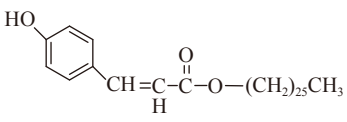


60 R = OH

61 R = O-Glc



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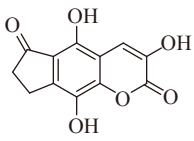

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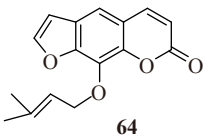

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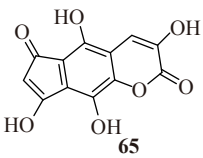

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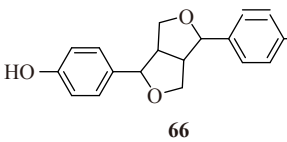

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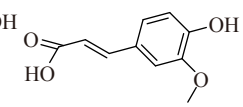

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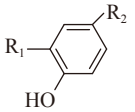

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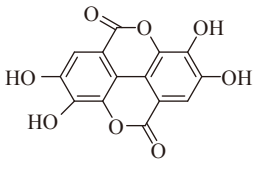

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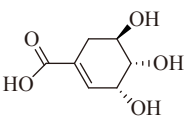

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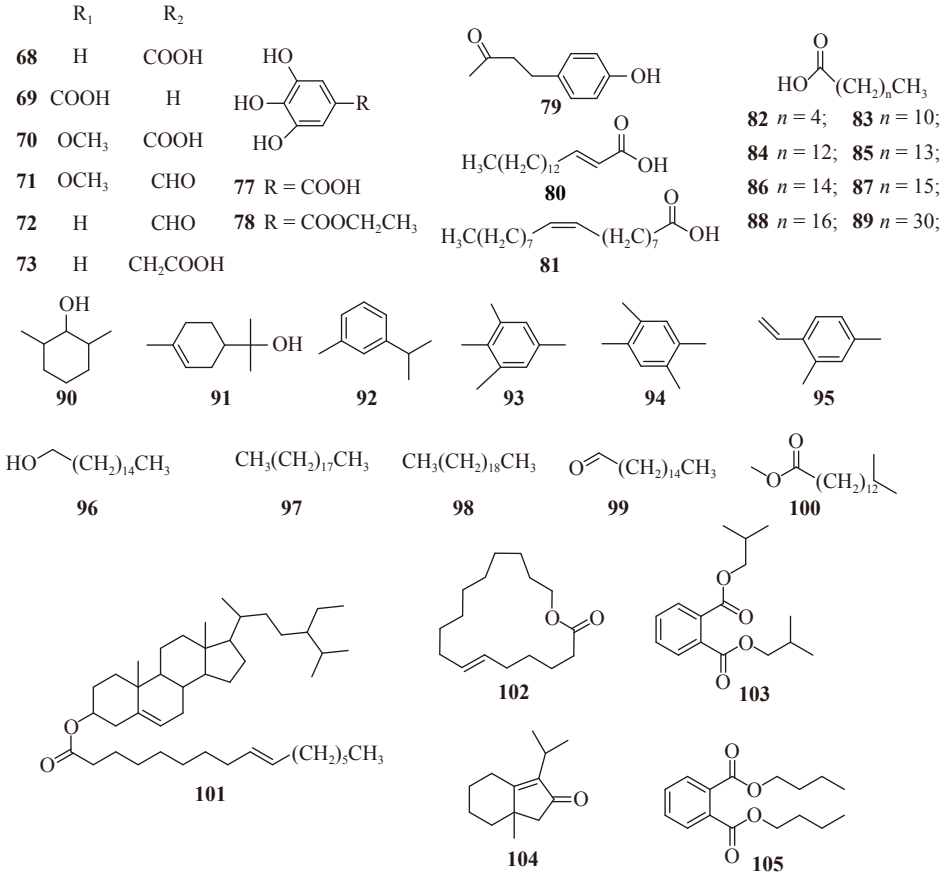

Fig. 2 Compounds 1–105 isolated from the fruits and leaves of *Rubus chingii* Hu

amount of reactive oxygen species in rat hepatocytes, as indicated by visualization by using a fluorescence probe 2V, 7V-dichlorofluorescein diacetate [80]. A glycoprotein with a molecular weight of 22.0 kDa was isolated from the fruits of *R. chingii*. The carbohydrate and protein contents were 81.42% ± 0.96% and 14.56% ± 1.21%, respectively. Glycoprotein could protect against oxidative damage *in vivo*, which was indicated by the enhanced superoxide dismutase (SOD) and catalase (CAT) activities and by decreased malondialdehyde (MDA) levels in the serum and kidney of D-galactose-induced aging mice [81]. Tian and Niu *et al*. [82, 83] investigated the antioxidant activity of raw glycoprotein from *R. chingii* fruits. Their results indicated that raw glycoprotein excellently eliminated 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radicals, superoxide anions, and hydroxyl ions in *vitro* and effectively improved the activities of SOD, CAT, and glutathione peroxidase (GSH-Px) in the serum, brain, and liver tissues of mice.

In some studies, free radical-generating systems in *vitro* were used to assess the natural chemicals for their antioxidative activities (as in the studies described below). Polysaccharides of *R. chingii* fruits (F-Ps) and leaves (L-Ps) displayed a dose-dependent DPPH free radical scavenging activity with concentrations of 62.5–1000 μg·mL^{-1}. The DPPH free radical scavenging activity of L-Ps was higher than that of F-Ps. When the *R. chingii* leaf polysaccharides concentration increased from 62.5 to 1000 μg·mL^{-1}, the DPPH free radical scavenging activity increased from 17.98% to 63.1% [84]. Ding *et al*. [68] reported that the ethanolic extract of *R. chingii* fruits and its *n*-butanol and ethyl acetate fractions exhibited obvious DPPH free radical scavenging with IC_{50} values of 17.9, 4.0, and 3.4 μg·mL^{-1}, respectively. 9 chemical components were purified from the *n*-butanol and ethyl acetate fractions of the ethanolic extract, among which tiliroside (**51**, IC_{50}: 13.47 μmol·L^{-1}), vanillic acid (**70**, IC_{50}: 34.9 μmol·L^{-1}), methyl (3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)-acetate (**53**, IC_{50}: 45.2 μmol·L^{-1}), and kaempferol (**42**, IC_{50}: 78.5 μmol·L^{-1}) exhibited higher DPPH free radical scavenging activity than did the positive control ascorbic acid (IC_{50}: 131.8 μmol·L^{-1}). Zhang *et al*. [85] reported that the flavonoid fraction from unripe fruits of *R. chingii* exhibited excellent oxygen-radical-absorbance capacity and DPPH free radical scavenging activity. The flavonoid fraction exhibited obvious DPPH free radical scavenging activity, with an inhibition rate of > 90% at a concentration of 0.2 mg·mL^{-1}, which was very close to the inhibition rate of the positive control ascorbic acid at the same concentration. Liu *et al*. [86] investigated the free radical scavenging activities of crude polysaccharides and refined polysaccharides from *R. chingii* fruits. In the simulated chemical reaction system *in vitro*, the polysacchar-

ide scavenging effect on OH· was studied using the Fenton reaction and that on O_2· was studied using the pyrogallol autoxidation method. The IC_{50} values of crude polysaccharides and refined polysaccharides to OH· were 1.37 and 0.91 mg·mL^{-1}, respectively, and the IC_{50} values of crude polysaccharides and refined polysaccharides to O_2· were 0.66 and 0.44 mg·mL^{-1}, respectively. The results of these tests, such as DPPH free radical scavenging test and oxygen radical absorbance capacity assay, are pure redox-chemistry with little relationship with antioxidant activity; thus, further investigations on its antioxidant activity and its mechanism are need to be performed.

Anti-inflammatory activity

Inflammation is the protective response to the infection injury. Chronically inadequate inflammation is intensively related to many diseases such as cancer [87], heart disease [88], diabetes mellitus [89] and Alzheimer's disease [90]. Lipopolysaccharide (LPS) is a strong immune activator that induces local inflammation. Macrophages play an important role in a host's defense against bacterial infection, and they are major cellular targets for LPS action. Stimulation of macrophages by LPS results in the expression of inducible nitric oxide synthase (iNOS), which catalyzes the production of large amounts of NO, an important messaging molecule, which in turn participates in the inflammatory response in macrophages [91, 92]. Many anti-inflammatory activities of chemical components of natural medicinal plants, including *R. chingii,* were evaluated in the inflammation model of LPS-induced RAW264.7 macrophages. F-Ps and L-Ps at a concentration of 400 μg·mL^{-1} reduced the generation of NO by 23.56% and 30.06%, respectively, in LPS-stimulated macrophage RAW 264.7 macrophages. The anti-inflammatory activity of F-Ps and L-Ps might be enhanced by inhibiting iNOS gene expression [84]. Four flavonoid glycosides from *R. chingii* fruits inhibited the NO production in LPS-treated RAW 264.7 macrophages. The NO production inhibitory rates increased in the following ascending order at a concentration of 100 μg·mL^{-1}: quercitrin (**41**, 21.6%) < hyperoside (**39**, 24.4%) < astragalin (**43**, 27.8%) < tiliroside (**51**, 30.4%). Tiliroside (100 μg·mL^{-1}) exhibited the strongest anti-inflammatory activity, which was very close to that of the positive control dexamethasone (50 μg·mL^{-1}). Tiliroside likely acts by suppressing extracellular signal-regulated kinase and Janus kinase activities, which leads to decreases in the levels of NO and the proinflammatory cytokines iNOS, tumor necrosis factor (TNF)-*α*, and interleukin (IL)-6 [65].

The anti-inflammatory activities of *R. chingii* are also related to the decrease of pro-inflammatory cytokines expressions (e.g., IL-6, TNF-*α*), and the inhibition of nuclear factor (NF)-*κ*B and mitogen-activate protein kinase (MAPK) signaling pathways. He *et al*. [93] reported the anti-inflammatory activity of goshonoside-F5 (5, GF5), an ent-labdane diterpene isolated from the dried unripe fruit of *R. chingii*. GF5 reduced IL-6 and TNF-*α* protein levels (IC_{50} = 17.04 and 4.09 μmol·L^{-1}, respectively) and mRNA levels in LPS-treated RAW 264.7 macrophage cells. GF5 administration also reduced NO and prostaglandin E2 (PGE2) production (IC_{50} = 3.84 and 3.16 μmol·L^{-1}, respectively) in a dose-dependent manner. It likely suppressed LPS-stimulated proinflammatory cytokines and inflammatory mediator production in RAW 264.7 cells by inhibiting the NF-*κ*B and MAPK pathway activation. Moreover, GF5 treatment reduced the inflammatory response and improved survival in LPS-induced endotoxemic mice. The improvement in survival was associated with lower TNF-*α* and IL-6 levels in the serum of GF5-treated mice than in untreated mice. Another *ent*-labdane diterpene obtained from *R. chingii* fruits, namely saponin goshonoside-G, also inhibited NO production in LPS-stimulated RAW 264.7 macrophages with an IC_{50} value 54.98 μmol·L^{-1} [51].

Antitumor activity

Research has been conducted recently on the antitumor activity of *R. chingii* and its bioactive constituents. Its extracts and constituents have been confirmed to exert the antitumor activity on human hepatocellular carcinoma cells (Bel-7402), human breast adenocarcinoma cells (MCF-7), and human lung adenocarcinoma cells (A549). F-Ps and L-Ps inhibited the proliferation of human hepatocellular carcinoma Bel-7402 cells and human breast adenocarcinoma MCF-7 cells in a concentration- and time-dependent manner. L-Ps exhibited obvious inhibitory activity on the growth of MCF-7 cells. The growth inhibition ratios for 48 and 72 h were 48.48% ± 0.55% and 66.30% ± 0.61%, respectively, at a concentration of 2 mg·mL^{-1} [84]. Zhang *et al*. [85] extracted alkaloids, saponins, flavonoids, and polysaccharides fractions from the unripe fruit of *R. chingii* and investigated their antitumor activity against human lung adenocarcinoma A549 cells. Among these four major constituents, saponins and flavonoids exhibited obvious cytotoxicity on the A549 cells. The inhibitory rates reached 62% and 65% for saponins and flavonoids, respectively, at a concentration of 200 μg·mL^{-1}. The inhibition rates were very close to that of the positive control 5-fluorouracil. The flavonoid fraction was then separated, and the major flavonoid tiliroside (**51**) was obtained. In the A549 cells, tiliroside suppressed cell proliferation with an IC_{50} values of 190.76 ± 3.18 μmol·L^{-1}. Moreover, tiliroside also induced apoptosis in the A549 cells, and the apoptosis rate increased from 1.7% to 21.8% after incubation with 200 μg·mL^{-1} of tiliroside for 48 h. Zhong *et al*. [52] investigated the cytotoxic activities of three labdane-type diterpenoids, 15,18-Di-*O*-*β*-D-glucopyranosyl-13(*E*)-ent-labda-7(8),13(14)-diene-3*β*, 15, 18-triol (**16**), 15,18-Di-*O*-*β*-D-glucopyranosyl-13(*E*)-ent-labda-8(9), 13(14)-diene-3*β*, 15, 18-triol (**14**) 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-3*β*, 15, 18-triol (**15**) against human colon cancer cells (HCT-8), human hepatoma 140 cancer cells (Bel-7402), human gastric cancer cells (BGC-823), human ovarian cancer cells (A2780), and A549. Diterpenoids 13 and 14 were inactive (IC_{50} >10 μmol·L^{-1}) to HCT-8, Bel-7402, BGC-823, A2780, and A549 cell lines. Diterpenoid 15 exhibited an antitumor effect (de-

creased cell viability) against human lung adenocarcinoma A549 cells ($IC_{50:}$ 2.32 μmol·L^{-1}). Matrix metalloproteinase 13 (MMP13) is a matrix metalloproteinase that is implicated in the processes of tumor growth, invasion, and metastasis [94-96] and is frequently overexpressed in malignant tumors [97]. Wang *et al*. [98] reported that the aqueous extract of *R. chingii* fruits inhibited MMP13 activity in a concentration-dependent manner from 0.005 to 0.10 μg·mL^{-1}, with an IC_{50} value of 0.036 μg·mL^{-1} *in vitro*, suggesting its potential antitumor activity.

Antifungal activity

Systemic fungal infections have become one of the main causes of morbidity and mortality in immunocompromised patients. Approximately 600 species of fungus are human pathogens, among which *Candida albicans* are the most common isolated fungus in immunocompromised patients [99, 100]. Han *et al*. [101] studied the antifungal activity of *R. chingii* 70% ethanol extract combined with fluconazole (FLC) against FLC-resistant *C. albicans* 100 in *vitro*. The lowest concentrations needed to inhibit 80% of fungal growth compared with the control for FLC and *R. chingii* extract were 0.0625–16 mg·mL^{-1} and 4.88–312.5 mg·mL^{-1}, respectively. The combination exhibited significant synergy; *C. albicans* cells were arrested mainly in the G_1 and S phases, and the ergosterol content of the cell membrane decreased. Moreover, the efflux of rhodamine 6G decreased with an increase in the *R. chingii* extract, suggesting that *R. chingii* extract reduces the efflux of *C. albicans* ATP-binding cassette transporter Cdr1p, which is considered the main contributor to azole resistance of *C. albicans* clinically [102, 103]. Shu *et al*. [50] reported that one ent-pimarane diterpenoid (14*β*, 16-epoxy-7-pimarene-3*α*, 15*β*-diol, **10**) isolated from *R. chingii* leaves inhibited the growth of four Candida species, namely *C. albicans, C. parapsilosis, C. glabrata, and C. krusei*, with minimum inhibitory concentration values of 36.8, 110.4, 55.2, and 73.6 μg·mL^{-1}, respectively.

Antithrombotic activity

Cardiovascular disease associated thrombosis is one of the most threatening causes of death worldwide (https://www.who.int/health-topics/cardiovascular-diseases/). Traditional Chinese remedies containing high doses of flavonoids, such as *Abelmoschus manihot* (L.) Medicus [104], *Ginkgo biloba* L. [105], *Carthamus tinctorius* L. [106], have been used as natural medicines to treat thrombotic diseases for a long time. Han *et al*. [67] investigated the antithrombotic effect of 70% ethanol fraction from the aqueous extract of *R. chingii* leaves *in vitro* and *in vivo*. *In vitro*, compared with the control group, the 70% ethanol fraction and 90% ethanol fraction significantly delayed the plasma recalcification time to 107.8 ± 2.68 s and 87.5 ± 3.86 s, respectively, in fresh rabbit blood, and the 70% ethanol fraction was even higher than the recalcification time of aspirin (99.5 ± 3.93 s). *In vivo*, compared with the control group (3.30 ± 0.41 min), 70% ethanol fraction at concentrations of 0.235 g·kg^{-1} (1.97 ± 0.45 min) and 0.470 g·kg^{-1} (2.19 ± 0.39 min) significantly reduced the recovery time of Kunming mice with acute pulmonary embolism stimulated by adenosine diphosphate. Further study indicated that the active compounds were three flavonoids of them: tiliroside (**51**), kaempferol (**42**), and quercetin (**44**).

Antiosteoporotic activity

Osteoporosis is a disease in which the density and quality of the bone are reduced, which results in an increased risk of fragility fracture [107]. It is a major health problem that affects 200 million people worldwide [108]. TCM theory holds that the kidney stores the essence, produces the marrow and nourishes the bones. In TCM theory, the major pathogenesis of osteoporosis is "deficiency of kidney essence, reduction of marrow and flaccidity of bones." It is an effective way to search effective antiosteoporotic substances from kidney-tonifying traditional Chinese drugs [109]. In the study of Liang *et al*. [61], the compounds rubusin B, rubusin A, kaempferol, and quercetin, which are isolated from the fruits of *R. chingii*, displayed antiosteoporotic effects to varying degrees. On the basis of osteoclasts and osteoblasts isolated from Wistar rats, kaempferol and quercetin exhibited potent stimulatory effects on osteoblastic proliferation and alkaline phosphatase activity in the concentration range of 0.01–1.00 ppm. Moreover, improvements of osteoblastic alkaline phosphatase activity in kaempferol and quercetin groups were even much stronger than that of positive control genistein in the concentration range of 0.10–1.00 ppm. Rubusin A (63) and rubusin B (65) displayed weak stimulatory effects on osteoblastic proliferation and alkaline phosphatase activity, but they significantly inhibited osteoclastic cell and bone resorption even at a concentration of 0.01 ppm. However, this study has used an only routine screening *in vitro*; further investigations are needed to clarify the exact molecular mechanism of their antiosteoporotic activity.

Hypoglycemic activity

Diabetes mellitus is a chronic disease characterized by an absolute or relative lack of insulin, leading to hyperglycemia. Numerous studies were performed to evaluate the hypoglycemic activity of natural compounds in some *in vitro* and *in vivo* models with varying degrees of insulin resistance and *β*-cells failure [110]. One of the most common models is the chemically induced diabetes model in rodents (streptozotocin- or alloxan-induced diabetic mice), which is convenient and relatively cheap and appropriate for evaluating compounds that reduce blood glucose through non-*β*-cell-dependent pathways [111]. Fan *et al*. [112] reported that the water extract of *R. chingii* leaves exhibited a prominent hypoglycemic activity in alloxan-induced diabetic mice and adults with a high level of blood glucose. In animal trials, the water extract with concentrations of 0.80 g·kg^{-1} body weight (bw) and 1.20 g·kg^{-1} bw reduced the fasting blood glucose level of mice significantly. Xie *et al*. [113] reported that the 70% ethanol extract of *R. chingii* fruits could improve glucose and blood lipid metabolisms in streptozotocin-induced diabetic rats and exhibited a protective effect on hepatic injury. Compared with the control group, treatment with the 70% ethanol

extract at a concentration of 2.0 g·kg^{-1} bw for 12 weeks significantly reduced the levels of fasting blood glucose (15.3 ± 3.7 *vs* 22.6 ± 2.5 mmol·L^{-1}), serum triglycerides (1.73 ± 0.54 *vs* 2.33 ± 0.57 mmol·L^{-1}), serum total cholesterol (2.95 ± 1.36 *vs* 4.67 ± 1.34 mmol·L^{-1}), serum low-density lipoprotein cholesterol (1.28 ± 0.38 *vs* 2.39 ± 0.76 mmol·L^{-1}), and serum fasting serum insulin (33.13 ± 5.14 *vs* 46.91 ± 3.81 mmol·L^{-1}) and enhanced levels of serum high-density lipoprotein cholesterol (1.32 ± 0.41 *vs* 0.75 ± 0.20 mmol·mL^{-1}). Moreover, the activity of SOD and GSH-Px increased; however, MDA was significantly decreased in the liver tissues (P < 0. 01). Hematoxylin and eosin staining indicated that the 70% ethanol extract significantly reduced fatty liver degeneration.

Protein tyrosine phosphatase 1B (PTP1B) is an important negative regulator of the insulin signaling pathway and has attracted considerable attention as a potential therapeutic target for type 2 diabetes mellitus [110]. Three ursane-type triterpenes, namely ursolic acid (**20**), 2-oxopomolic acid (**17**), and 2*α*, 19*α*-dihydroxy-3-oxo-urs-12-en-28-oic acid (**18**), have been isolated from *R. chingii* fruits. A PTP1B inhibition test *in vitro* indicated that the aforementioned ursane-type triterpenes inhibited PTP1B in a concentration-dependent manner with IC_{50} values of 7.1 ± 1.0, 23.7 ± 2.7, and 52.3 ± 7.2 μmol·L^{-1}, respectively. Moreover, ursolic acid was a non-competitive PTP1B inhibitor, and 2-oxopomolic acid and 2*α*, 19*α*-dihydroxy-3-oxo-urs-12-en-28-oic acid were mixed-type inhibitors [54].

Central nervous system regulating activity

Alzheimer disease is a common neurodegenerative disorder that slowly destroys thinking and memory capability and severely affects millions of people in old age. Some studies have been conducted on *R. chingii* extract used in the central nervous system. The chloroform and ethyl acetate fractions of the 80% ethanol extract of the unripe fruit of *R. chingii* protected against learning and memory injury in mice caused by D-galactose combined with hydrocortisone in kidney yang deficiency Alzheimer's disease rats. The chloroform and acetate fractions at a concentration of 12 g·kg^{-1} bw significantly reduced the cortex acetylcholinesterase (AChE) activity (0.99 ± 0.26 and 0.83 ± 0.25, respectively; control group, 1.24 ± 0.20 U·mg^{-1}; P < 0.01) and increased the choline acetyltransferase (ChAT) activity (122.16 ± 10.72 and 116.10 ± 14.75, respectively; control group, 79.62 ± 10.26 U·g^{-1}; P < 0.01) in model rats after treatment for 4 weeks. Moreover, the chloroform and ethyl acetate fractions increased the total number of cells in the hippocampus CA1 area (47.89 ± 11.08 and 45.72 ± 7.26, respectively; control group, 32.81 ± 4.58 cells; P < 0.01), reduced the cell necrosis rate (91% ± 4% and 65% ± 10%, respectively; control group, 96% ± 3%; P < 0.01), and reduced the Pser404-tau-positive cells of the hippocampus CA1 area (3.92 ± 0.96 and 4.27 ± 0.98, respectively; control group, 35.67 ± 7.98 cells; P < 0.01). The results indicated that the active fractions improved learning and memory abilities, likely by reducing the AChE activity, enhancing the ChAT activity, protecting the neurons of hippocampal CA1 area, and reducing the tau protein expression [114]. Another study suggested that the chloroform and acetate fractions at a concentration of 12 g·kg^{-1} bw can also shorten rats' escape latency (15.78 ± 2.26 and 12.56 ± 6.77, respectively; control group, 36.70 ± 18.06 s; P < 0.01) and increase the times of crossing the platform (space exploration ability) in the Morris water maze (4.33 ± 3.01 and 4.67 ± 1.37, respectively; control group, 1.17 ± 0.75 s; P < 0.01). The serum testosterone level is also significantly increased (0.59 ± 0.14 and 2.06 ± 1.19 s, respectively; control group, 0.21 ± 0.15 s) in model rats after treatment for 4 weeks [115]. Xia *et al*. [116] reported that the chloroform fraction and ethyl acetate fraction of unripe fruit of *R. chingii* extract at the concentration of 12 g·kg^{-1} bw shortened rats' escape latency (15.78 ± 2.26 and 12.56 ± 6.77 respectively; control group, 36.70 ± 18.06 s, P < 0.01) and enhanced rats' space exploration ability (4.33 ± 3.01 and 4.67 ± 1.37 respectively; control group, 1.17 ± 0.75 s, P < 0.01) in the Morris water maze test of aged rats. In addition, the activities of AChE, SOD, and CAT increased and the MDA content decreased in the brains of aged rats. Simultaneously, the two fractions reduced ChAT and increased the GSH-Px activity. These results suggested that the improved activity was related to the enhancement of the cholinergic function and alleviation of free radicals in the brains of aged rats.

Toxicity

The safety of TCM deserves increased scientific attention. In general, the minimal toxicity dosage and side effects need to be determined for herbal medicine products. Tang *et al*. [117] investigated the safety and toxicity of the aqueous extract of *R. chingii* leaves by a series of acute, mutagenic and subchronic toxicological tests. The acute toxicity test showed that the maximum tolerated oral dose of its aqueous extract was greater than 20.0 g·kg^{-1} bw in mice. No mutagenicity was found, as judged by mouse bone marrow cell micronucleus test, Ames test and mouse sperm abnormality test. In the subchronic study, no deaths, no remarkable changes in general appearance, and no clinical signs, including food and water consumption, body weight, organ weight, and hematological, biochemical and histopathological parameters, were found in rats after gavaging 2.5, 5.0, and 10.0 g·kg^{-1}·d^{-1} for 90 days. To date, there is only one study, described above, on *R. chingii* safety. Although *R. chingii* has long been recognized as a safe medicinal herb and functional food, considering its wide consumption, it is important to determine if any toxicological effects can occur with its chronic and subchronic consumption. However, safety evaluation for this plant remains lacking. Thus, safety verification of *R. chingii*, especially for its fruits, is needed prior to its pharmacological exploitation and clinical application.

Quality control

Unripe *R. chingii* fruit was used as the raw material of *R. chingii* in the "Chinese Pharmacopoeia". Qualitative and

quantitative analyses of the unripe fruits of *R. chingii* were lacking in the "Chinese Pharmacopoeia" prior to the 2015 version. According to "Chinese Pharmacopoeia 2015", tiliroside should be tested using TLC in qualitative identification. Furthermore, the contents of ellagic acid and kaempferol-3-rutinoside in the fruits of *R. chingii* should be not be less than 0.20% and 0.03%, respectively, when using high-performance liquid chromatography (HPLC). Quality markers should be used to select the characteristic and active components, which are significant in the assessment of the quality and efficacy of the medicinal material. However, no data are currently available regarding whether tiliroside, ellagic acid, and kaempferol-3-rutinoside represent the pharmacological activities and are the best choice for the characteristic substances of *R. chingii*. Moreover, TCM is truly complex with many contributing components. One or a few main ingredients barely reflect the quality of a Chinese medicine. Thus, additional studies are warranted to determine whether such qualitative and quantitative analytical methods are scientific and whether there exist better choices that can more effectively control the quality of *R. chingii*. He *et al*. [118] established the HPLC evaporative light scattering detection method for the determination of the goshonoside-F5 content in unripe fruits of *R. chingii.* Chen and Miao [119, 120] established an HPLC fingerprint analysis method for the unripe fruits of *R. chingii.* These two methods may offer some useful insights for the establishment of an *R. chingii* quality standard. In summary, to establish a scientific and reasonable quality standard for *R. chingii*, additional relevant in-depth phytochemical and pharmacological studies are required.

Discussions and conclusions

R. chingii has been used as a medicine in China for more than 1500 years, and people have witnessed its efficacy. *R. chingii* has been used to treat diseases mainly associated with kidney deficiency. In the present review, 105 chemical constituents from the fruits and leaves of *R. chingii* are summarized. These compounds mainly include terpenoids, flavonoids, steroids, alkaloids, phenylpropanoids, phenolics, and organic acids. Among them, terpenoids, including diterpenoids and triterpenoids, are the characteristic substances of *R. chingii*. Existing modern pharmacological research has revealed that extracts or agents from this plant have various pharmacological properties, including antioxidant, anti-inflammatory, antitumor, antifungal, antithrombotic, antiosteoporotic, hypoglycemic, and central nervous system-regulating effects. Despite the rapid development and outstanding progress in the chemistry and pharmacology of *R. chingii* in recent years, research on *R. chingii* is still in the initial stages, and some research challenges must be further investigated.

First, previous studies have showen the great potential of *R. chingii* for the treatment of various ailments; however, the majority of studies have focused only on crude and poorly characterized extracts, which are a complex mixture of chemical constituents. The particular pharmacological property may be due to a single chemical, and also may be generated from multiple ingredients working in concert, so further research is needed to elucidate its bioactive constituents. If the former, the active chemical constituents of *R. chingii* must be determined using bioassay-guided isolation strategies. Specifically, terpenoids are considered as the characteristic substances of *R. chingii*. However, modern pharmacological studies on terpenoid compounds are insufficient. Future studies should research the pharmacological properties of the terpenoid monomers of *R. chingii* and the mechanism(s) of its action. If the latter, using a systems biology approach can infer correlations of multiple components to understand the mechanism of pharmacological activities from many different angles, including multiple targets, multiple actions and multiple levels. Either way, the 105 monomers contained in *R. chingii* which might contribute directly or indirectly to its clinical efficacy and some of these compounds have the potential to be developed as novel and effective pharmaceutical drugs.

Second, according to the empirical practical descriptions of its unripe fruits, *R. chingii* is used as a single drug or an essential ingredient in some TCM formulations mainly for improving or eliminating different types of kidney-related diseases, such as spermatorrhea, impotence, frequent micturition, infertility, and sterility. *R. chingii* formulations are still in clinical use for the aforementioned conditions. TCM theory holds that the kidney stores the essence, which produces marrow which nourishes bone and brain. The antiosteoporotic activity and central nervous system-regulating activity of *R. chingii* extract may correspond to its traditional use for "nourishing kidney" and "enriching essence". However, much modern pharmacological research is focused on anti-inflammatory, antitumor, antifungal, antithrombotic, and hypoglycemic effects, which seem irrelevant to its traditional uses of *R. chingii.* Therefore, further studies should elucidate the relationship between the modern pharmacological activities and traditional usages of *R. chingii*, which would contribute to expanding its clinical usage and comprehensive use. In addition, most of the studies have focused on the pharmacological activities of the fruits of *R. chingii,* but ignored its leaves. According to chemical constituents' analysis, diterpenoids, flavonoids and phenolics are existed in the leaves of *R. chingii*, which implies that there may be some pharmacological effects to be explored.

Third, some of the pharmacological activities assessed so far, such as antioxidant, anti-inflammatory, antitumor, and antiosteoporotic activities, were routine screenings *in vitro*, which are too general and too preliminary, and even some might be irrational to be used to explain the pharmacological effects. For example, some antioxidant studies mentioned above speculated that agents are able to react with reactive oxygen species or free radicals *in vitro*, so they can exhibit the antioxidant activity *in vivo*. It is noticeable that there is no evidence for whether a substance has an impact on function in human or animal studies, although its antioxidant activit-

ies are observed *in vitro*. Whether chemical antioxidant assays such as the DPPH free radical scavenging assay are of pharmacological relevance is unclear. Therefore, further investigations of its antioxidant activity and its mechanism of action need to be carried out, and similarly for the other activities, such as anti-inflammatory, antitumor, and antiosteoporotic activities.

R. chingii is an effective traditional medicine and edible nutritious foodstuff, and considerable historical and contemporary information has revealed that the fruits of *R. chingii* possess numerous health benefits, such as blackening of hair and improvement of eyesight. Therefore, the fruits of *R. chingii* also have considerable potential as nutrient supplements. According to ancient Chinese documents, the leaves of *R. chingii* have unique advantages, such as in the treatment of glaucoma and relief of red-eye pain. The aforementioned information may guide the exploration of additional potential therapeutic effects of *R. chingii* in the future.

In conclusion, this paper provides detailed and up-to-date information on *R. chingii* and systematically reviews its botanical characterizations, traditional uses, chemical constituents, pharmacological activities, and toxicity, highlighting the importance of this plant. Despite the rapid development and outstanding progress in the chemistry and pharmacology of *R. chingii* in recent years, research on *R. chingii* is still in the initial stages, and some research challenges must be addressed. Further studies to elucidate the bioactive constituents and the plant's pharmacological properties, especially the mechanism of activities to illustrate the relationship between the modern pharmacological activities and traditional uses, will undoubtedly be the major focus of *R. chingii* research. The safety of use of this species remains poorly studied, and robust quality standards have not been established. It is anticipated that this review can supply fundamental data for the further study of *R. chingii*. and contribute to the development of its clinical usage.

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