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REVIEW ARTICLE

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Coptidis Rhizoma: a comprehensive review of its traditional uses, botany, phytochemistry, pharmacology and toxicology

Jin Wang[a]*, Lin Wang[a]*, Guan-Hua Lou[a], Hai-Rong Zeng[a], Ju Hu[a], Qin-Wan Huang[a], Wei Peng[a] and Xiang-Bo Yang[b]

[a]College of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, China; [b]Ya'an Xun Kang Pharmaceutical Co., Ltd, Ya'an, China

ABSTRACT

Context: Coptidis rhizome (CR), also known as *Huanglian* in Chinese, is the rhizome of *Coptis chinensis* Franch., *C. deltoidea* C.Y. Cheng et Hsiao, or *C. teeta* Wall (Ranunculaceae). It has been widely used to treat bacillary dysentery, diabetes, pertussis, sore throat, aphtha, and eczema in China.

Objectives: The present paper reviews the latest advances of CR, focusing on the botany, phytochemistry, traditional usages, pharmacokinetics, pharmacology and toxicology of CR and its future perspectives.

Methods: Studies from 1985 to 2018 were reviewed from books; PhD. and MSc. dissertations; the state and local drug standards; PubMed; CNKI; Scopus; the Web of Science; and Google Scholar using the keywords *Coptis*, Coptidis Rhizoma, *Huanglian*, and goldthread.

Results: Currently, 128 chemical constituents have been isolated and identified from CR. Alkaloids are the characteristic components, together with organic acids, coumarins, phenylpropanoids and quinones. The extracts/compounds isolated from CR cover a wide pharmacological spectrum, including antibacterial, antivirus, antifungal, antidiabetic, anticancer and cardioprotective effects. Berberine is the most important active constituent and the primary toxic component of CR.

Conclusions: As an important herbal medicine in Chinese medicine, CR has the potential to treat various diseases. However, further research should be undertaken to investigate the clinical effects, toxic constituents, target organs and pharmacokinetics, and to establish criteria for quality control, for CR and its related medications. In addition, the active constituents, other than alkaloids, in both raw and processed products of CR should be investigated.

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KEYWORDS
Huanglian; morphology; alkaloids; berberine; pharmacokinetics; toxicity

Introduction

Coptidis rhizome (CR), also known as *Huanglian* in Chinese, is the rhizome of *Coptis chinensis* Franch. (*Weilian* in Chinese), *C. deltoidea* C.Y. Cheng et Hsiao (*Yalian* in Chinese), or *C. teeta* Wall. (*Yunlian* in Chinese) (Ranunculaceae) (Chinese Pharmacopoeia Commission 2015). Moreover, *C. japonica* Makino and its variants are also used in Japan (Cho et al. 2001). Large quantities of CR are consumed in Asian countries, such as China, Japan, Malaysia, Singapore and India, but only a small amount is used in European countries (Kong et al. 2013).

CR has been used to treat various inflammatory disorders and related diseases for a thousand years, and has functions of clearing heat, drying dampness and detoxification according to the traditional Chinese Medicinal theory. The medicinal use of this plant was first listed in *Shennong's Classic of Materia Medica* in China, which was written during the Han Dynasty. More than 32,000 Chinese Medical formulas mention CR, usually in the form of a powder, pill, decoction or tablet (Wu et al. 2015). It is often utilized to treat diarrhoea, vomiting, abdominal fullness, jaundice, high fever coma, toothache, diabetes and eczema. Modern studies have demonstrated that CR has wide pharmacological activities, including antibacterial, antifungal, antiviral, antihepatic steatosis, anti-atherosclerosis, antimyocardial ischaemia/reperfusion injury, antidiabetic, antiarrhythmia, antihypertention, anti-inflammation, antioxidation and antitumour effects (Ma and Ma 2013; Wang 2016; Dan et al. 2017; Liu D et al. 2017). Currently, over 120 chemical components have been isolated and identified from CR. Apart from its main composition of alkaloids, it also contains organic acids, lignans, flavones, volatile oils, etc. (Yoshikawa et al. 1997a, 1997b; Wang et al. 2014; Chen et al. 2016). The present review provides the overview of CR from 1985 to 2018 in terms of its botany, phytochemistry, traditional usages, pharmacology, pharmacokinetics and toxicology. We also offer some perspectives about the future research into this herbal medicine.

Traditional usages

The rhizome is the main medicinal part of CR, and it is processed by 28 methods before clinical use, some of which are taken from ancient Chinese medicines books (Table 1). From these methods, we observed that CR processing has changed from simple to complex and then from complex to simple (Mei 2008). Nowadays, CR is commonly processed with wine, *Zingiber*

CONTACT Qin-Wan Huang hqwan2163@163.com; Wei Peng pengwei002@126.com
*These authors contributed equally to this work.

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Table 1. Different processing methods of CR.

Processing method	Purpose of processing	Dynasty	Reference
Rubbing the fibrous roots with cloth, washing	Removing non-medicinal parts and impurities to ensure curative effect	Before the Tang Dynasty	(Lei 1985)
Stir-baking to dark brown	Enhancing the efficacy of digestion and invigorating the function of spleen	Song Dynasty	(Wang 1991)
Carbonizing by stir-frying	Producing hemostatic effect	Qing Dynasty	(Chen 2006)
Stir-baking with loess	Invigorating the function of spleen andstomach	Jin Yuan Period,Ming Dynasty	(Zhu 2012)
Stir-frying with wine	Treating insomnia, sore mouth, red and swelling eyes	Song Dynasty, Jin Yuan Period	(Zhu 2015)
Stir-frying with Ginger	Enhancing the effect preventing vomitting, and expelling phlegm	Song Dynasty	(Wang 1991)
Stir-frying with bile	Enhancing the function of clearing the fire of the liver and galllbladder	Ming Dynasty	
Immersing into rice water	Strengthening the role of nourishing the spleen and harmonizing the spleen and stomach	Song Dynasty, Qing Dynasty	(Qian & Wang 2008)
Stir-baking with Evodiae Fructus	Curing diarrhea	Yuan Dynasty	(Zhu 2012)
Stir-baking with Rhizoma Zingiberis Recens	Enhancing the effect of preventing vomitting	Song Dynasty	(Dong 2003; Tang 2011)
Stir-baking with Sophorae Flos	Treatment of dysentery	Ming Dynasty	(Zhang 1996)
Steaming with wine	Curing diarrhea	Ming Dynasty	
Steaming with milk	Curing acute conjunctivitis	Ming Dynasty	(Han 1985)

officinale Rosc. (Zingiberaceae) juice, and *Evodia rutaecarpa* (Juss.) Benth. (Rutaceae) to exert different functions including treating insomnia, sore mouth, red and swelling eyes, preventing vomiting, expelling phlegm and curing diarrhoea (Lei and Dun 2002; Lu 2004; Li 2013; Chinese Pharmacopoeia Commission 2015).

The medicinal value of CR is worth affirming. Relevant statistics show that in 13 prescriptions before the Song Dynasty, more than 32,000 Chinese Medical formulae mentioned CR. Currently, CR is commonly used as a main traditional Chinese medicine (TCM) to treat respiratory diseases (including tuberculous empyema, whooping cough, and pulmonary candidiasis caused by pneumonia), digestive diseases (including diarrhoea, chronic colitis and upper gastrointestinal infection), paediatric diseases (including hyperthermia of infantile external sensation, dyspepsia and urticaria), dermatological diseases (including acne, psoriasis, dermatitis and tinea pedis), and nervous system diseases (Wu et al. 2015). CR has been employed in the form of powders, pills or decoctions (Table 2).

Botany

Coptis chinensis (Figure 1(A)) is a perennial herb with yellow, branched rhizomes. The leaves are slightly leathery, with three lobes (Xiao 2002). The scapes are 12–25 cm high. In addition, 3–8 flowers are clustered into a dichasium or pleiochasium. The five sepals, 9–12.5 mm in length, 2–3 mm in width, are greenish yellow and oblong ovate. There are approximately 20 stamens with 8–12 carpels, which are slightly curved outside. The 6–12 follicles are 6–8 mm in length with a thin handle. There are 7–8 brown, oblong seeds that are 2 mm long and 8 mm wide. Flowering occurs from February to March, and the fruit is commonly harvested from April to June. It is distributed in Sichuan, Guizhou, Hunan, Hubei, and southern Shaanxi in China. This plant grows in mountain forests or valleys at an altitude of approximately 500–2000 m (Flora 2004).

C. deltoidea (Figure 1(B)) is also a perennial herb with unbranched or few branched yellow rhizomes. The 3–11 leaves are oval and slightly leathery, are 16 cm long and 15 cm wide and are finely divided into three parts. The one or two scapes are slightly longer than the leaves. The plant produces 4–8 flowers, which are clustered into a blue-green inflorescence. Sepals are yellow-green, narrow ovoid, 8–12.5 mm long, and 2–2.5 mm wide. There are approximately 20 stamens, which are about half the length of the petals. The anther is yellow, and the filament is narrowly linear. The flowering period is March and April and the fruit are harvested from April to June. It is native to the areas of Emei and Hongya in Sichuan province. This plant grows in mountain forests with an altitude approximately 1600–2200 m (Flora 2004).

C. teeta (Figure 1(C)) is an often used as a folk medicine in Yunnan Province of China. It is a perennial herb with yellow rhizomes yellow, dense internodes and mostly fibrous roots. The blade comprises oval-shaped triangles that are 6–12 cm long and 5–9 cm wide, with a triple fissure. *C. teeta* has one or two scapes and is 15–25 cm high during the fruiting period. It has a blue-green inflorescence with 3–5 flowers. The yellow-green, oval calyx is 7.5–8 mm long and 2.5–3 mm wide. The anther is about 0.8 mm long and filament is 2–2.5 mm long. *C. teeta* is commonly distributed in Yunnan and Tibet provinces of China, and in Burma. *C. teeta* commonly grows in the shade of cold and damp mountainous areas with an altitude of approximately 1500–2300 m (Flora 2004) .

The major morphological differences among the rhizomes of these three plants is that *Weilian* is curved, branched, clustered, and shaped like chicken's feet; *Yalian* is less branched and cylindrical; while *Yunlian* is the smallest and is shaped like a scorpion's tail. In this review, we will mainly discuss the advances in research into CR from *Coptis chinensis*, which is the most common source for CR.

Phytochemistry

The first investigation concerning the chemical components of CR, which succeeded in isolating berberine (**1**), was reported in 1862 from *C. teeta* (Perrins 1862). To date, over 100 chemical constituents have been isolated and identified. Alkaloids are the most abundant among these chemical components and are considered as the main active ingredients of CR. Besides alkaloids, CR contains organic acids, coumarins, phenylpropanoids, quinones and other chemical components. In this section, the structures of the main compounds of CR are described and drawn (Table 3; Figures 2–10).

Table 2. The traditional and clinical uses of CR in China.

Preparation	Main compositions	Traditional and clinical uses	References
An Gong Niu Huang Pills	Coptidis Rhizoma, Bovis Calculus, Condensed powder of Bubali Corun, Moschusm or Artificial Moschusm, Margarita, Cinnabaris, Realgar, Scutellariae Radix, Gardeniae Fructus, Curcumae Radix, Syntheticum Borneolum	Curing febrile convulsions, delirious, and gibberish	(Chinese Pharmacopoeia Commission 2015)
Dang Gui Long Hui Pills	Coptidis Rhizoma, Angelicae Sinensis Radix, Gentianae Radix et Rhizoma, Rhei Radix et Rhizoma, Scutellariae Radix, Phellodendri Chinensis Cortex, Aloe, Ineigo Naturalis, Gardeniae Fructus, Aucklandiae Radix, Artificial Moschusm	Curing dizziness, tinnitus, deafness, rib pain, abdominal distension pain and constipation	
Fu Fang Qing Dai Pill	Coptidis Rhizoma, Cnidii Frucutus, Sophorae Flavescentis Radix, Pseudolaricis Radix, Catechu, Alumen	Treating mycotic vaginitis, trichomonas vaginitis, and nonspecific vaginitis	
Huang Lian Shang Qing Pills	Coptidis Rhizoma, Gardeniae Fructus, Forsythiae Fructus, Viticis Fructus, Saposhnikoviae Radix, Schizonepetae Spica, Angelicae Dahuricae Radix, Scutellariae Radix, Rhei Radix et Rhizoma, Chrysanthemi Flos, Menthae Haplocalycis Herba, Phellodendri Chinensis Cortex, Platycodonis Radix, Chuanxiong Rhizoma	Treating dizziness, tooth pain, tongue sores, sore throat, ear pain tinnitus and constipation	
Huang Lian Yang Gan Pills	Coptidis Rhizoma, Rhizoma Picrohizae, Scutellariae Radix, Phellodendri Chinensis Cortex, Gentianae Radix et Rhizoma, Bupleuri Radix, Citri Reticulatae Pericarpium Viride, Equiseti Hiemalis Herba, Buddlejae Flos, Leonuri Fructus, Cassiae Semen, Haliotidis Concha	Treating red sore, eye, blurred vision	
Kai Guang Fu Ming Pills	Coptidis Rhizoma, Gardeniae Fructus, Phellodendri Chinensis Cortex, Scutellariae Radix, Rhei Radix et Rhizoma, Saposhnikoviae Radix, Chrysanthemi Flos, Gentianae Radix et Rhizoma, Scrophulariae Radix, Paeoniae Radix Rubra, Alismatis Rhizoma, Rehmanniae Radix	Clearing heat and improving eyesight	
Mu Xiang Bing Lang Pills	Coptidis Rhizoma, Aucklandiae Radix, Arecae Semen, Aurantii Fructus, Citri Reticulatae Pericarpium, Citri Reticulatae Pericarpium Viride, Cyperi Rhizoma, Sparganii Rhizoma, Curcumae Rhizoma, Phellodendri Chinensis Cortex, Rhei Radix et Rhizoma, Natrii Sulfas, Pharbitidis Semen	Treating abdominal distension pain and constipation	
Niu Huang Qian Jin Powder	Coptidis Rhizoma, Scorpio, Bombyx Batryticatus, Bovis Calculus, Cinnabaris, Borneolum Syntheticum, Arisaema Cum Bile, Gastrodiae Rhizoma, Glycyrrhizae Radix et Rhizoma	Clearing heat and detoxifying, calming nerves, curing children convulsion with high fever, hand and foot convulsions	
Qin Lian Tablets	Coptidis Rhizoma, Phellodendri Chinensis Cortex, Forsythiae Fructus, Scutellariae Radix, Paeoniae Radix Rubra, Glycyrrhizae Radix et Rhizoma	Treating headache and red eye, mouth and nose sores, hot dysentery, abdominal pain	
Shen Shuai Ning Capsules	Coptidis Rhizoma, Radix Pseudostellariae, Praeparatum Pinelliae Rhizoma, Citri Reticulatae Pericarpium, Poria, Rhei Radix et Rhizoma, Glycyrrhizae Radix et Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, Achyranthis Radix, Carthami Flos	Curing nausea, vomiting, poor appetite, bad urine, stool viscous	
Wan Shi Niu Huang Qing Xin Pills	Coptidis Rhizoma, Bovis Calculus, Cinnabaris, Scutellariae Radix, Gardeniae Fructus, Curcumae Radix	Curing high fever irritability, insanity and children febrile convulsion	
Wu Mei Pills	Coptidis Rhizoma, Mume Fructus, Asari Radix et Rhizoma, Zingiberis Rhizoma, Aconiti Lateralis Radix Praeparata, Zanthoxyli Pericarpium, Cinnamomi Ramulus, Ginseng Radix et Rhizoma, Phellodendri Chinensis Cortex, Angelicae Sinensis Radix	Curing abdominal pain, headache, mania, vomiting, and limbs cold.	
Xiao Ke Ping Tablets	Coptidis Rhizoma, Ginseng Radix et Rhizoma, Trichosanthis Radix, Asparagi Radix, Astragali Radix, Salviae Miltiorrhizae Radix et Rhizoma, Lycii Fructus, Astragali Complanati Semen, Puerariae Lobatae Radix, Anemarrhenae Rhizoma, Galla Chinensis, Schisandrae Chinensis Fructus	Curing diabetes	
Xiang Lian Pills	Coptidis Rhizoma, Aucklandiae Radix	Curing enteritis, and bacillary dysentery, relieving pain	
Xiong Ju Shang Qing Pills	Coptidis Rhizoma, Chuanxiong Rhizoma, Scutellariae Radix, Viticis Fructus, Menthae Haplocalycis Herba, Schizonepetae Spica, Ligustici Rhizoma et Radix, Saposhnikoviae Radix, Angelicae Dahuricae Radix, Chrysanthemi Flos, Gardeniae Fructus, Forsythiae Fructus, Platycodonis Radix, Glycyrrhizae Radix et Rhizoma, Notopterygii Rhizoma et Radix	Treating migraine headache, nasal flow toothache, sore throat	

(*continued*)

Table 2. Continued.

Preparation	Main compositions	Traditional and clinical uses	References
Yi Qing Granules	Coptidis Rhizoma, Rhei Radix et Rhizoma, Scutellariae Radix	Treating pharyngitis, tonsil inflammation and gum inflammation	
Zhu Che Pills	Coptidis Rhizoma, Zingiberis Rhizoma Praeparatum, Angelicae Sinensis Radix, Moschus	Nourishing Yin and stopping dysentery, curing abdominal pain, diarrhea	
Zuo Jin Pills	Coptidis Rhizoma, Euodiae Fructus	Purging fire, soothing the liver, reconciling the intestines and stomach, analgesiastomach ache, mouth bitter noise, and vomiting	
Niu Huang Qing Re Powder	Coptidis Rhizoma, Scutellariae Radix, Gardeniae Fructus, Curcumae Radix, Bovis Calculus, Bubali Corun, Cinnabaris, Borneolum Syntheticum	Treating high fever spasm, limbs twitch, irritability restless, and phlegm turbid congestion	(Zhong 1991)
Niu Huang Xing Nao Pills	Coptidis Rhizoma, Bovis Calculus, Bubali Corun, Borneolum Syntheticum, Scutellariae Radix, Gardeniae Fructus, Moschusm, Cinnabaris, Margarita, Curcumae Radix	Curing high fever, coma convulsion, irritable restlessness, infantile convulsionand insomnia	(Zhong 1998)
Qing Wei Huang Lian Pills	Coptidis Rhizoma, Glycyrrhizae Radix et Rhizoma, Platycodonis Radix, Gypsum Fibrosum, Anemarrhenae Rhizoma, Moutan Cortex, Trichosanthis Radix, Forsythiae Fructus, Scutellariae Radix, Gardeniae Fructus, Phellodendri Chinensis Cortex	Curing tongue sores, and sore throat	(Zhong 1998)
San Huang Pills	Coptidis Rhizoma, Rhei Radix et Rhizoma, Huang Cao	Curing dysentery, vomiting , hemoptysis and constipation	
Xiao Er Qing Re Zhen Jing Powder	Coptidis Rhizoma, Arisaema Cum Bile, Scorpio, Bombyx Batryticatus, Glycyrrhizae Radix et Rhizoma, Bovis Calculus, Cinnabaris, Borneolum Syntheticum, Bambusae Concretio Silicea	Curing hot convulsion, hand-foot convulsions, cough, irritability and thirst	(Zhong 1991)
San Huang Qing Jie Pills	Coptidis Rhizoma, Scutellariae Radix, Forsythiae Fructus, Phellodendri Chinensis Cortex, Lonicerae Japonicae Flos	Curing fever, cough, sore throat, hot leaching and diarrhea	(Guo 2002)
Xie Li Xiao Pills	Coptidis Rhizoma, Atractylodis Rhizoma, Alba Paeoniae Radix, Aucklandiae Radix, Euodiae Fructus, Magnoliae Officinalis Cortex, Arecae Semen, Aurantii Fructus, Citri Reticulatae Pericarpium, Alismatis Rhizoma, Poria, Glycyrrhizae Radix et Rhizoma	Treating acute enteritis, colitis, and dysentery	
Huang Lian Jie Du Pills	Coptidis Rhizoma, Phellodendri Chinensis Cortex, Scutellariae Radix, Rhei Radix et Rhizoma, Talcum, Clematidis Armandii Caulis, Gardeniae Fructus	Treating sore mouth, headache, constipation, red eyes, heartburn, sore throat,	
Geng Nian Xin Capsules	Coptidis Rhizoma, Cinnamomi Cortex, Alpiniae Oxyphyliae Fructus, Lycii Fructus, Corni Fructus, Ligustri Lucidi Frucrus, Cuscutae Semen, Acori Tatarinowii Rhizoma, Rehmanniae Radix, Polygalae Radix, Ziziphi Spinosae Semen, Citri Reticulatae Pericarpium, Alismatis Rhizoma	Curing heart palpitations, insomnia, dizziness, tinnitus, and backache	(Chinese Pharmacopoeia Commission 2008)

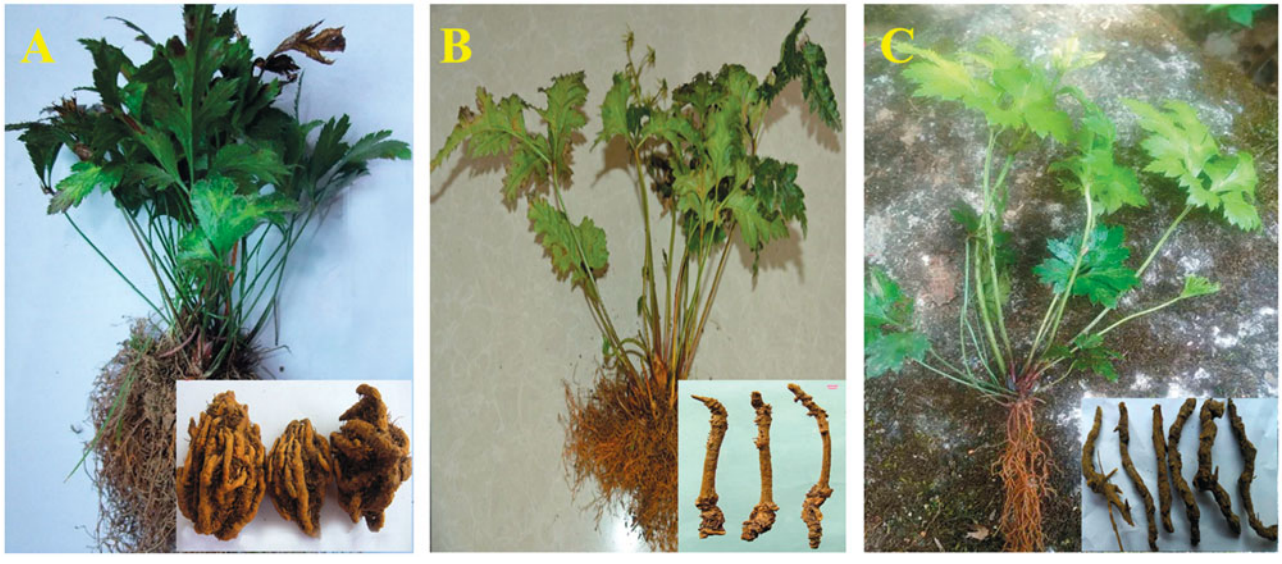


Figure 1. The whole plants and rhizomes of *C. chinensis* (A), *C. chinensis* (B) and *C. teeta* (C).

Table 3. Partial list of chemical compounds isolated from CR.

Classification	Number	Ingredient name	Reference
Alkaloids	**1**	Berberine	(Noguchi et al. 1978)
	2	Berberrubine	(Li ZF et al. 2012)
	3	Coptisine	(Wang et al. 2014)
	4	Palmatine	
	5	Epiberberine	(Mizuno et al. 1992)
	6	Columbamine	(Ikuta and Itokawa 1989)
	7	Tetradehydroscoulerine	(Chen et al. 2008)
	8	Jatrorrhizine	(Li ZF et al. 2012)
	9	Groenlandicine	
	10	Berberastine	(Li ZF et al. 2012)
	11	Worenine	
	12	8-Oxyberberine	(Wang et al. 2014)
	13	8-Oxycoptisine	
	14	3-Hydroxy-2-methoxy-9,10-methylenedioxy-8-oxyprotoberberine	(Zhao et al. 2010)
	15	8-Oxyepiberberine	(Yang et al. 2014)
	16	8-Oxyberberrubine	
	17	(−)-5-Hydroxyl-8-oxyberberine	(Wang et al. 2014)
	18	(+)-5-Hydroxyl-8-oxyberberine	
	19	Tetrahydroberberine	(Wang et al. 2014)
	20	8,13-Dioxocoptisine hydroxide	(Yang et al. 2014)
	21	1,3-Dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one	(Wang et al. 2007)
	22	Noroxyhydrastinine	
	23	Corydaldine	(Ma et al. 2013)
	24	Thalifoline	(Li ZF et al. 2012)
	25	6-([1,3]Dioxolo[4,5-g]isoquinoline-5-carbonyl)-2,3-dimethoxy benzoic acid methyl ester	(Wang et al. 2014)
	26	Berbithine	
	27	Coptisonine	(Yang et al. 2014)
	28	Tetrandrine	
	29	Obamegine	
	30	Magnoflorine	(Tomita and Kura 1956)
	31	Sanguinarine	(Mizuno et al. 1988)
	32	Norsanguinarine	
	33	Oxysanguinarine	
	34	6-Acetonyl-5,6-dihydrosanguinarine	
	35	Chilenine	(Yang et al. 2014)
	36	*Z*-*N*-Ferulyltyramine	(Li ZF et al. 2012)
	37	*E*-*N*-Feruloyltyramine	(Ma H et al. 2013)
	38	3-Hydroxy-1-(4-hydroxyphenethyl) pyrrolidine-2,5-dione	(Li ZF et al. 2013)
	39	4′-[Formyl-5-(hydroxymethyl)-1*H*-pyrrol-1-yl] butanoate	(Ma H et al. 2013)
	40	8,9-Dihydroxy-1,5,6,10-β-tetrahydro-2H-pyrrolo[2,1-α]-isoquinolin-5-one	(Li, et al. 2012)
	41	Ehyl-2-pyrrolidinone-5(*S*)-carboxylate	
	42	Methyl-5-hydroxy-2-pyridinecarboxylate	
	43	1*H*-indole-3-carboxaldehyde	
	44	Choline	(Chen L et al. 2012)
Lignans	**45**	Woorenogenin	(Chen et al. 2016)
	46	Woorenoside I	(Yoshikawa et al. 1995)
	47	Longifolroside A	(Meng et al. 2013)
	48	Woorenoside II	(Yoshikawa et al. 1995)
	49	Woorenoside V	
	50	Woorenoside III	
	51	Woorenoside IV	
	52	(+)-Pinoresinol	
	53	(+)-Medioresinol	
	54	(+)-Pinoresinol glucoside	
	55	(+)-Pinoresinol-4,4′-*O*-β-D-diglucopyranoside	(Yoshikawa et al.1997)
	56	(+)-Syringaresinol glucoside	(Meng et al. 2013)
	57	(+)-Lariciresinol	(Hirano et al. 1997)
	58	(±)-5,5′-Dimethoxylariciresinol	(Li XG et al. 2012)
	59	(+)-5′-Methoxylariciresinol	(Chen L et al. 2012)
	60	(+)-Lariciresinol glucoside	(Chen et al. 2016)
	61	7*S*, 8*R*, 8′*R*-(+)-Lariciresinol-4,4′-*O*-β-D-diglucopyranoside	(Yoshikawa et al.1997)
	62	Lanicepside A	(Chen et al. 2016)
	63	9-Acetyl lanicepside B	
	64	(+)-Isolariciresinol	
	65	Isolarisiresinol-9-*O*-β-D-glucopyranoside	(Li XG et al. 2012)
	66	Woorenoside XI	(Yoshikawa et al.1997)
	67	Cleomiscosin A	(Mizuno et al. 1992)
	68	Aquillochin	(Min et al. 1987)
	69	2,3-bis[(4-Hydroxy-3,5-dimethoxyphenyl)-methyl]-1,4-butanediol	
	70	secoisolariciresinol	(Li XG et al. 2012)
	71	Erythro-gaiacylglycerol-8-*O*-4′-(coniferylalcohol) ether	(Chen L et al. 2012)
	72	Threo-guaiacylglycerol-8-*O*-4′-(coniferyl alcohol) ether	
	73	Woorenoside X	(Yoshikawa et al.1997)

(*continued*)

Table 3. Continued.

Classification	Number	Ingredient name	Reference
	74	Dihydrodehydrodiconiferyl alcohol	(Li XG et al. 2012)
	75	Wooreno	(Yoshikawa et al.1997)
Simple phenylpropanoids	**76**	*Z*-Octadecyl cafeate	(Yang et al. 2014)
	77	*E*-3-Methoxycinnamic acid	(Ma H et al. 2013)
	78	Ferulic acid	(Li XG et al. 2012)
	79	Ethyl ferulate	(Yoshikawa et al. 1995)
	80	*N*-Butyl ferulate	(Ma H et al. 2013)
	81	*p*-Hydroxyphenethyl *E*-ferulate	(Hirano et al. 1997)
	82	*E*-3,4-Dimethoxycinnamic acid	(Ma H et al. 2013)
	83	4-*O*-Feruloylquinic acid	(Li XG et al. 2012)
	84	Methyl 4-*O*-feruloylquicinate	(Li XG et al. 2012)
	85	Ethyl 4-*O*-feruloylquicinate	(Ma H et al. 2013)
	86	4-*O*-Feruloylquinic acid butyl ester	(Li XG et al. 2012)
	87	5-*O*-Feruloylquinic acid	(Li XG et al. 2012)
	88	Methyl 5-*O*-feruloylquicinate	
	89	Ethyl 5-*O*-feruloylquicinate	
	90	5-*O*-Feruloylquinic acid butyl ester	(Ma H et al. 2013)
	91	Chlorogenic acid	(Chen L et al. 2012)
	92	Methyl 3-*O*-feruloylquicinate	(Li XG et al. 2012)
	93	*N*-Butyl 3-*O*-feruloylquicinate	(Ma H et al. 2013)
	94	3-(4′-Hydroxyphenyl)-(2*R*)-lactic acid	(Li XG et al. 2012)
	95	3-(3′,4′-Hydroxyphenyl)-(2*R*)-lactic acid	(Yahara et al. 1985)
	96	3-(3′,4′-Dihydroxyphenyl)-(2*R*)-lactic acid-4′-*O*-β-D-glucopyranoside	
	97	Methyl-3-(4′-*O*-β-D-glucopyranosyl-3′,4′-dihydroxyphenyl)-lactate	(Yoshikawa et al.1997)
	98	Methyl-3,4-dihydroxyphenyl lactate	(Li XG et al. 2012)
	99	Ethyl-3,4-dihydroxyphenyl lactate	(Ma H et al. 2013)
	100	*N*-Butyl-3,4-dihydroxyphenyl lactate	
	101	3-(2,3,4-Trihydroxyphenyl) propanoic acid	(Li XG et al. 2012)
Flavonoids	**102**	6,8-Dimethyl-3,5,7-trihydroxyfavone	(Meng et al. 2013)
	103	Rhamnetin	(Chen L et al. 2012)
	104	Wogonin	
	105	7,4′-Dihydroxy-5-methoxyfavanone	(Min et al. 1987)
	106	2′,4,4′-Trihydroxy-6′-methoxydihydrochalcone	
	107	Coptiside I	(Fujiwara et al. 1976)
	108	Coptiside II	
	109	Woorenoside XII	(Yoshikawa et al.1997)
Other compounds	**110**	Limonin	(Wang et al. 2007)
	111	3,4-Dihydroxyphenylethyl alcohol	(Li XG et al. 2012)
	112	3′,4′-Dihydroxyphenethyl alcohol 1-*O*-β-D-glucopyranoside	(Yahara et al. 1985)
	113	3,5-Dihydroxyphenethyl alcohol-3-*O*-β-D-glucopyranoside	(Meng et al. 2013)
	114	Protocatechuic aldehyde	(Ma H et al. 2013)
	115	Gentisic acid-5-*O*-β-D-glucopyranoside	(Yahara et al. 1985)
	116	Apocynol	(Ma H et al. 2013)
	117	1,2-Dihydroxy-benzene	(Li ZF et al. 2012)
	118	Protocatechuic acid	(Meng et al. 2013)
	119	Vanillic acid	(Li ZF et al. 2012)
	120	Vanillic acid-4-*O*-β-D-glucopyranoside	
	121	Protocatechuic acid methyl ester	(Ma H et al. 2013)
	122	Protocatechuic acid ethyl ester	(Wang et al. 2012)
	123	Woorenoside VI	(Yoshikawa et al.1997)
	124	Woorenoside VII	
	125	Woorenoside VIII	
	126	Woorenoside IX	
	127	*cyclo*-(Phe-Val)	(Li ZF et al. 2012)
	128	*cyclo*-(Phe-Leu)	
	129	β-Sitosterol	(Yang et al. 2014)

Alkaloids

Alkaloids are the main active ingredients of coptidis, and isoquinoline alkaloids account for a large proportion, with berberine (**1**) as the most representative compound. Berberine is one of the most abundant ingredients (Cooper et al. 1970) at 4.5–8%, although this varies in different varieties of CR. In addition to berberine, CR contains over 30 different kinds of isoquinoline alkaloids, which can be divided into the following subtypes according to their structures: protoberberines, simple isoquinolines, aporphines and benzylisoquinolines (Figures 2–5).

Protoberberines

The protoberberine alkaloids are derived from benzylisoquinolines through phenolic oxidation and coupling with the isoquinoline N-methyl group, which becomes the 'berberine bridge' carbon. Tetracyclic rings, which are based on the dibenzo quinolizidine system, form the main matrices of protoberberine (Cooper et al. 1970). According to the position of the double bond and whether the nitrogen atom has a positive charge, the protoberberines can be divided into 10 subtypes, as shown in Figure 2. The following is a list of 20 representative protoberberine compounds that can be found in CR. Among these subtypes, type 3 is the most

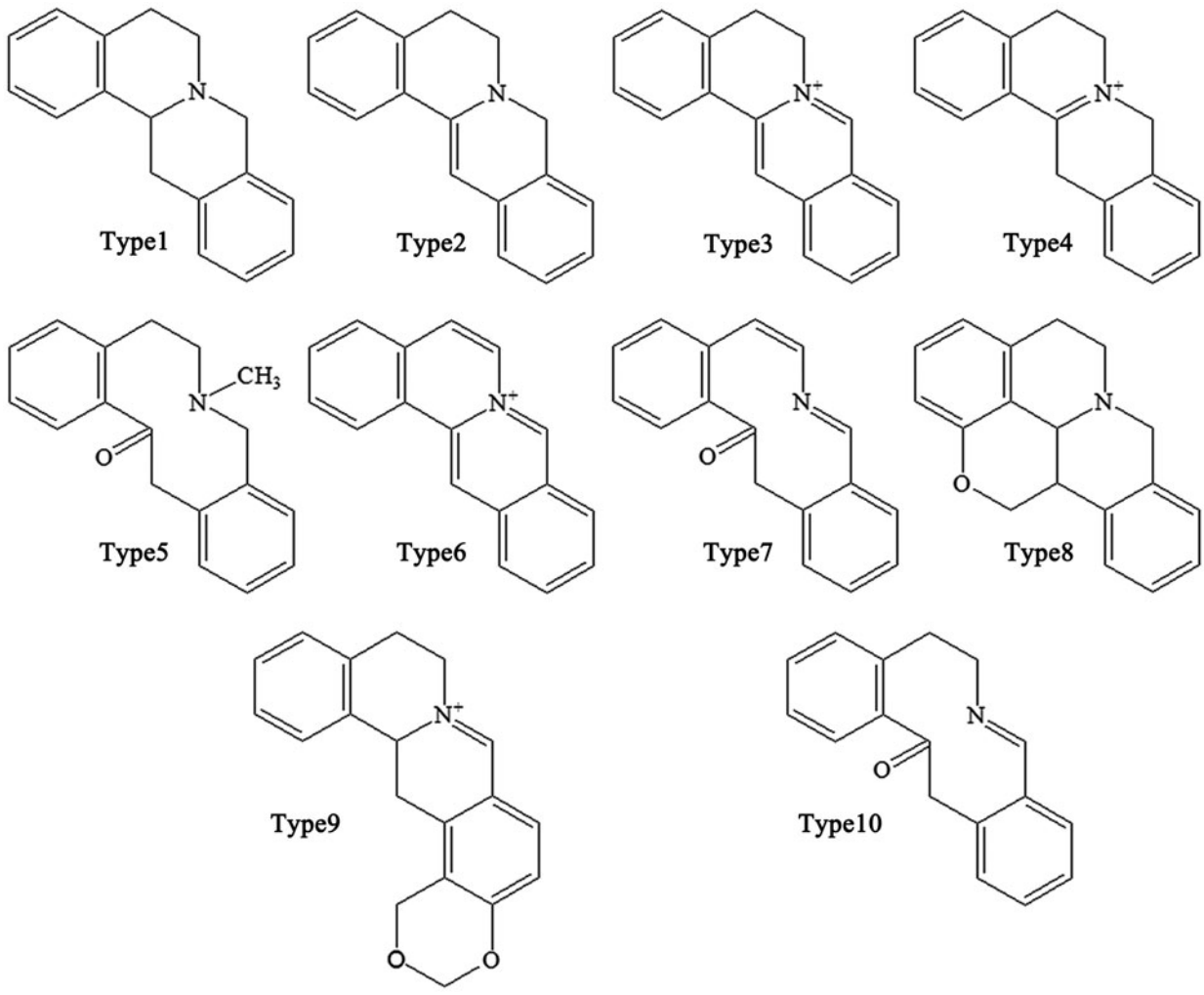


Figure 2. Subtypes of protoberberines in Coptidis Rhizoma.

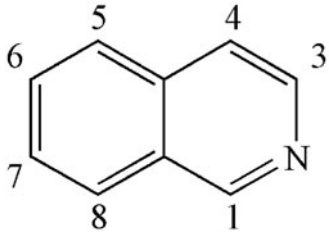


Figure 3. Matrices of isoquinolines in Coptidis Rhizoma.

common one in CR: Berberine (**1**), berberrubine (**2**), coptisine (**3**), palmatine (**4**), epiberberine (**5**), columbamine (**6**), tetradehydroscoulerine (**7**), jatrorrhizine (**8**), groenlandicine (**9**), berberastine (**10**), worenine (**11**), 8-oxyberberine (**12**), 8-oxycoptisine (**13**), 3-hydroxy-2-methoxy-9,10-methylenedioxy-8-oxyprotoberberine (**14**), 8-oxyepiberberine (**15**), 8-oxyberberrubine (**16**), (-)-5-hydroxyl-8-oxyberberine (**17**), (+)-5-hydroxyl-8-oxyberberine (**18**), tetrahydroscoulerine (**19**), and 8,13-dioxocoptisine hydroxide (**20**) (Yoshikawa et al. 1995; Wang et al. 2007; Li ZF et al. 2012; Fan et al. 2014; Wang et al. 2014).

Simple isoquinolines

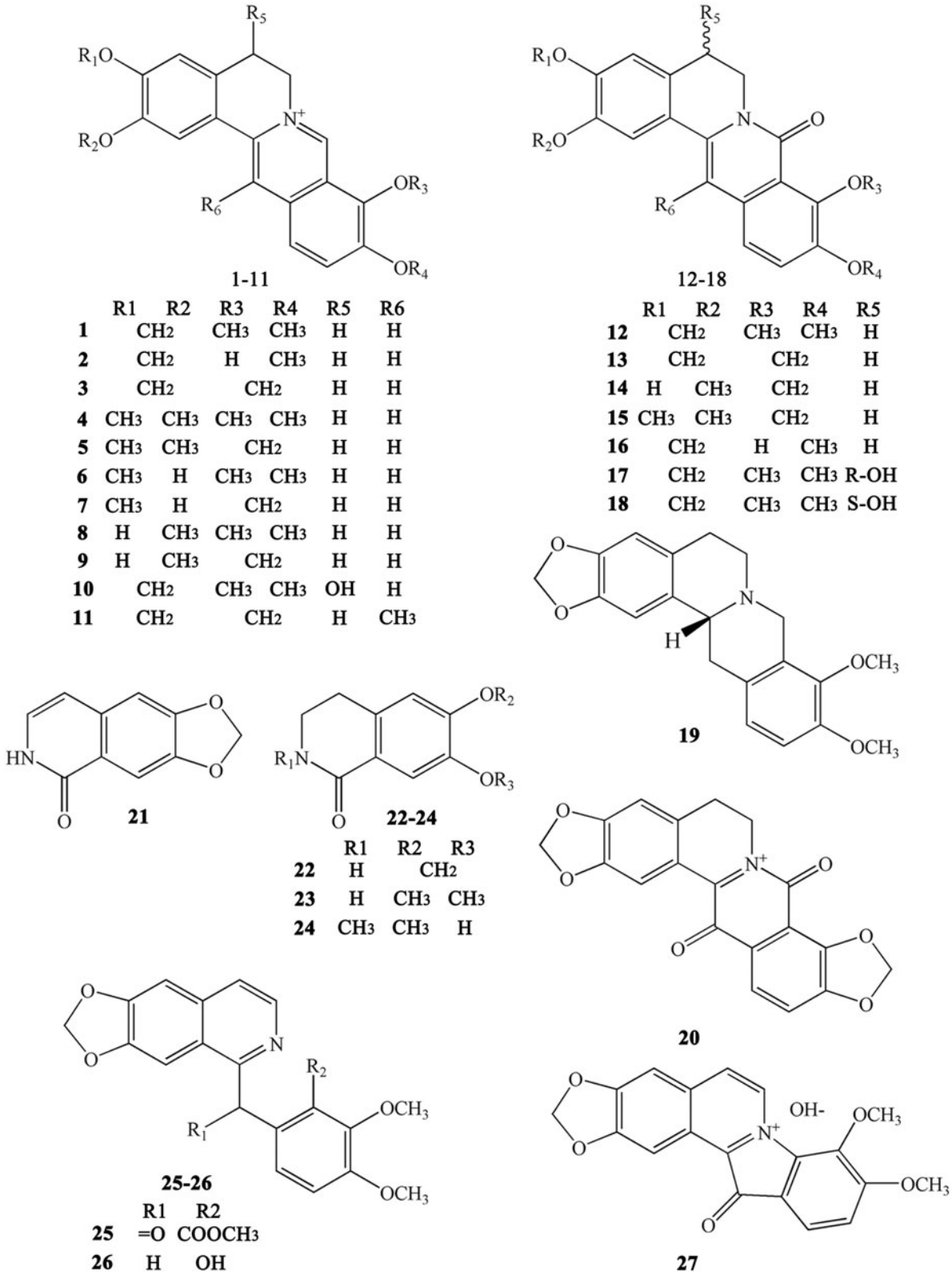
Alkaloids belonging to this subtype are fused together by a benzene ring and a pyridine; the nitrogen atom is in position 2 (which differs from quinoline) (Figure 3). Simple isoquinolines usually have a smaller in molecular weight and have no complex branched chains. The simple isoquinolines in CR include 1,3-dioxolo[4,5-g]isoquinolin-5(6H)-one (**21**), noroxyhydrastinine (**22**), corydaldine (**23**), and thalifoline (**24**) (Wang et al. 2007; Li ZF et al. 2012; Fan et al. 2014).

Benzylisoquinolines

Benzylisoquinolines are divided into 1-benzylisoquinolines and *bis*-benzylisoquinolines. 1-Benzylisoquinolines are compounds with isoquinoline matrices and a benzyl group at position 1. Furthermore, *bis*-benzylisoquinolines are formed by a combination of two 1-benzylisoquinolines *via* 1-3 ether bonds, such as 6-([1,3]dioxolo[4,5-g]isoquinoline-5-carbonyl)-2,3-dimethoxy benzoic acid methyl ester (**25**), berbithine (**26**), coptisonine (**27**), tetrandrine (**28**), and obamegine (**29**) (Wang et al. 2007).

Other alkaloids

CR also contains other subtypes of alkaloids, such as magnoflorine (**30**) (Tomita and Kura 1956), which is an active ingredient belonging to the aporphine alkaloids. Moreover, some benzophenanthridine alkaloids can also be found in certain specific CR varieties. For example, sanguinarine (**31**), norsanguinarine (**32**),



	R1	R2	R3	R4	R5	R6
1	CH_2		CH_3	CH_3	H	H
2	CH_2		H	CH_3	H	H
3	CH_2		CH_2		H	H
4	CH_3	CH_3	CH_3	CH_3	H	H
5	CH_3	CH_3	CH_2		H	H
6	CH_3	H	CH_3	CH_3	H	H
7	CH_3	H	CH_2		H	H
8	H	CH_3	CH_3	CH_3	H	H
9	H	CH_3	CH_2		H	H
10	CH_2		CH_3	CH_3	OH	H
11	CH_2		CH_2		H	CH_3

	R1	R2	R3	R4	R5
12	CH_2		CH_3	CH_3	H
13	CH_2		CH_2		H
14	H	CH_3	CH_2		H
15	CH_3	CH_3	CH_2		H
16	CH_2		H	CH_3	H
17	CH_2		CH_3	CH_3	R-OH
18	CH_2		CH_3	CH_3	S-OH

	R1	R2	R3
22	H	CH_2	
23	H	CH_3	CH_3
24	CH_3	CH_3	H

	R1	R2
25	=O	$COOCH_3$
26	H	OH

Figure 4. Alkaloids numbered **1–27** in Coptidis Rhizoma.

oxysanguinarine (**33**), and 6-acetonyl-5,6-dihydrosanguinarine (**34**) can be found in *C. japonica* (Maiti et al. 1982). CR also includes some small alkaloids, which are not representative compounds, such as chilenine (**35**) (Fan et al. 2014), *Z-N*-ferulyltyramine (**36**), *E-N*-feruloyltyramine (**37**), 3-hydroxy-1-(4-hydroxyphenethyl) pyrrolidine-2,5-dione (**38**), and 4′-[formyl-5-(hydroxymethyl)-1-pyrrol-1-yl] butanoate (**39**) (Wang et al. 2007); and 8,9-dihydroxy-1,5,6,10-β-tetrahydro-2H-pyrrolo[2,1-α]-isoquinolin-5-one (**40**), ethyl-2-pyrrolidinone-5(*S*)-carboxylate (**41**) (Li et al. 2012), methyl-5-hydroxy-2-pyridinecarboxylate (**42**), 1*H*-indole-3-carboxaldehyde (**43**), and choline (**44**) (Chen et al. 2012; Li XG et al. 2012; Li ZF et al. 2012; Ma H et al. 2013).

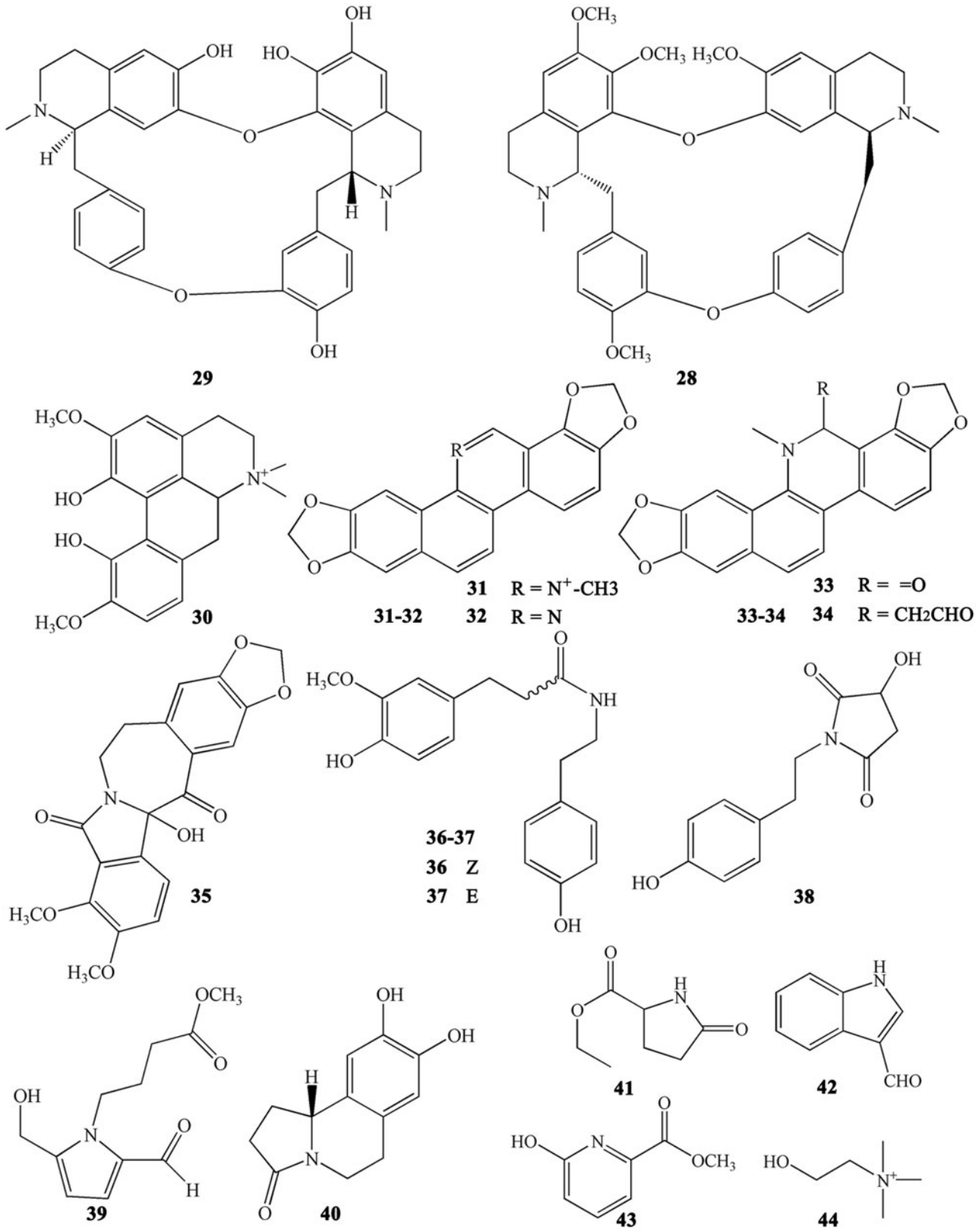


Figure 5. Alkaloids numbered **28–44** in Coptidis Rhizoma.

Phenylpropanoids

Phenylpropanoids are a class of compounds that are linked together by a benzene ring and three-carbon chains. They are a large class of organic compounds that exist widely exist in natural medicines and can be subdivided into many different subclasses. The molecular weight of phenylpropanoids in CR varies greatly, as do their structures. Both phenylpropanoids and their glycosides were reported in CR.

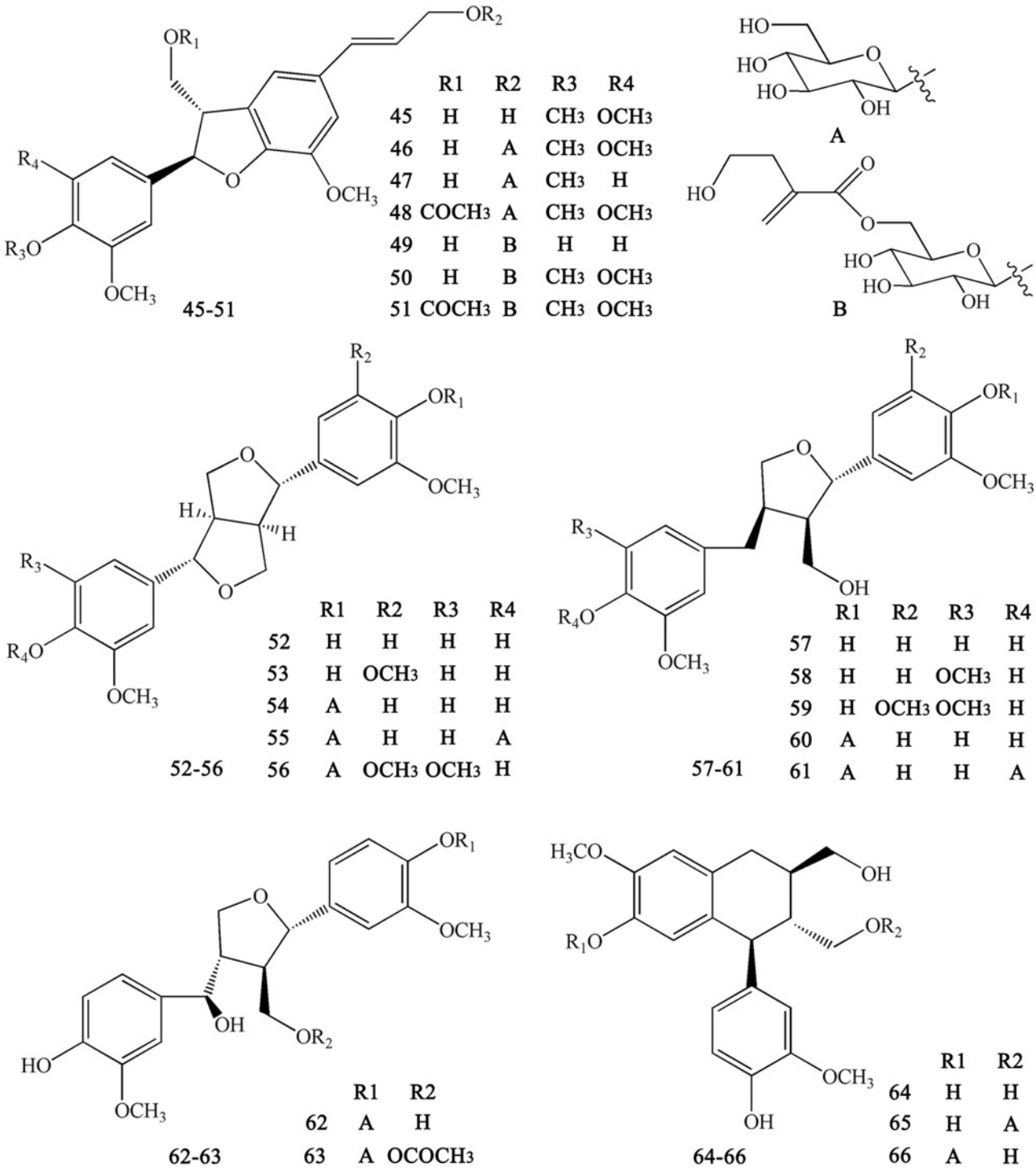


Figure 6. Lignans numbered **45–66** in Coptidis Rhizoma.

Lignans

Lignans are important natural constituents with various pharmacological activities. Special kinds of phenylpropanoids, which are a combination of two or more simple phenylpropanoids, were comprehensively investigated and isolated from CR (Min et al. 1987;; Hirano et al. 1997; Yoshikawa 1997a; Chen L et al. 2012; Li XG et al. 2012; Wang et al. 2012). These constituents include woorenogenin (**45**), woorenoside I (**46**), longifolroside A (**47**), woorenoside II (**48**), woorenoside V (**49**), woorenoside III (**50**), woorenoside IV (**51**), (+)-pinoresinol (**52**), (+)-medioresinol (**53**), (+)-pinoresinol glucoside (**54**), (+)-pinoresinol-4,4′-*O*-β-D-diglucopyranoside (**55**), (+)-syringaresinol glucoside (**56**), (+)-lariciresinol (**57**), (±)-5,5′-dimethoxylariciresinol (**58**), (+)-5′-methoxylariciresinol (**59**), (+)-lariciresinol glucoside (**60**), 7*S*, 8 *R*, 8′*R*-(+)-lariciresinol-4,4′-*O*-β-D-diglucopyranoside (**61**), lanicepside A (**62**), 9-acetyl lanicepside B (**63**), (+)-isolariciresinol (**64**), isolarisiresinol-9-*O*-β-D-glucopyranoside (**65**), woorenoside XI (**66**), cleomiscosin A (**67**), aquillochin (**68**), 2,3-bis-[(4-hydroxy-3,5-dimethoxyphenyl)-methyl]-1,4-butanediol (**69**), secoisolariciresinol (**70**), erythro-gaiacylglycerol-8-*O*-4′-

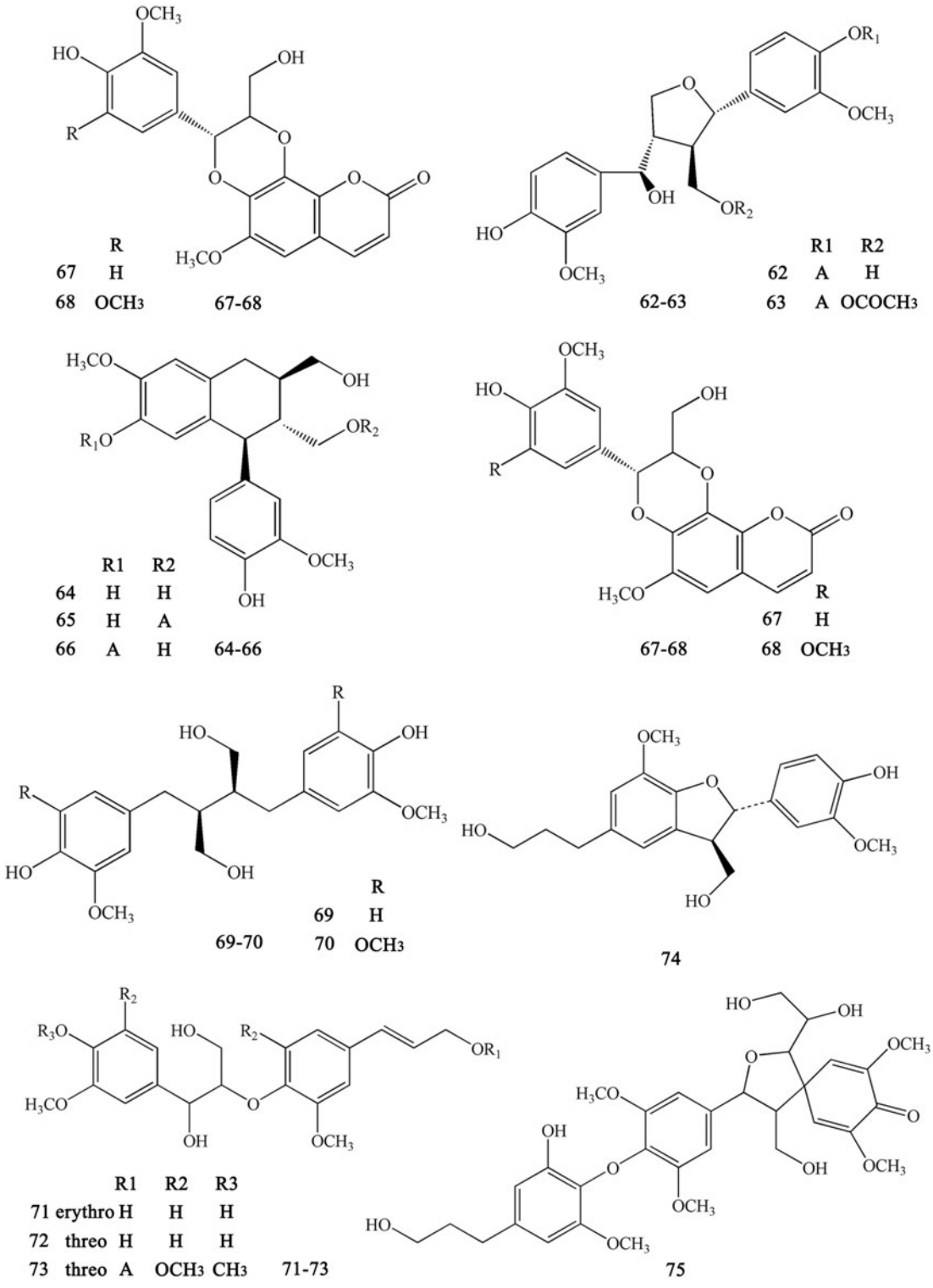


Figure 7. Lignans numbered **67–75** in Coptidis Rhizoma.

(coniferylalcohol) ether (**71**), threo-guaiacylglycerol-8-*O*-4′-(coniferyl alcohol) ether (**72**), woorenoside X (**73**), dihydrodehydrodiconiferyl alcohol (**74**), and wooreno (**75**) (Figures 6–7).

Simple phenylpropanoids

Ferulic acid and its derivatives are the most common simple phenylpropanoids in herbal medicine. In addition to ferulic acid, we can also found other simple phenylpropanoids. These derivatives usually form esters with carboxyl groups (Yahara et al. 1985; Yoshikawa et al. 1995, 1997a; Hirano et al. 1997; Chen L et al. 2012; Li et al. 2012; Meng et al. 2013; Fan et al. 2014). These compounds include *Z*-octadecyl cafeate (**76**), *E*-3-methoxycinnamic acid (**77**), ferulic acid (**78**), ethyl ferulate (**79**), *N*-butyl ferulate (**80**), *p*-hydroxyphenethyl *E*-ferulate (**81**), *E*-3,4-dimethoxycinnamic acid (**82**), 4-*O*-feruloylquinic acid (**83**), methyl 4-*O*-feruloylquicinate (**84**), ethyl-4-*O*-feruloylquicinate (**85**),

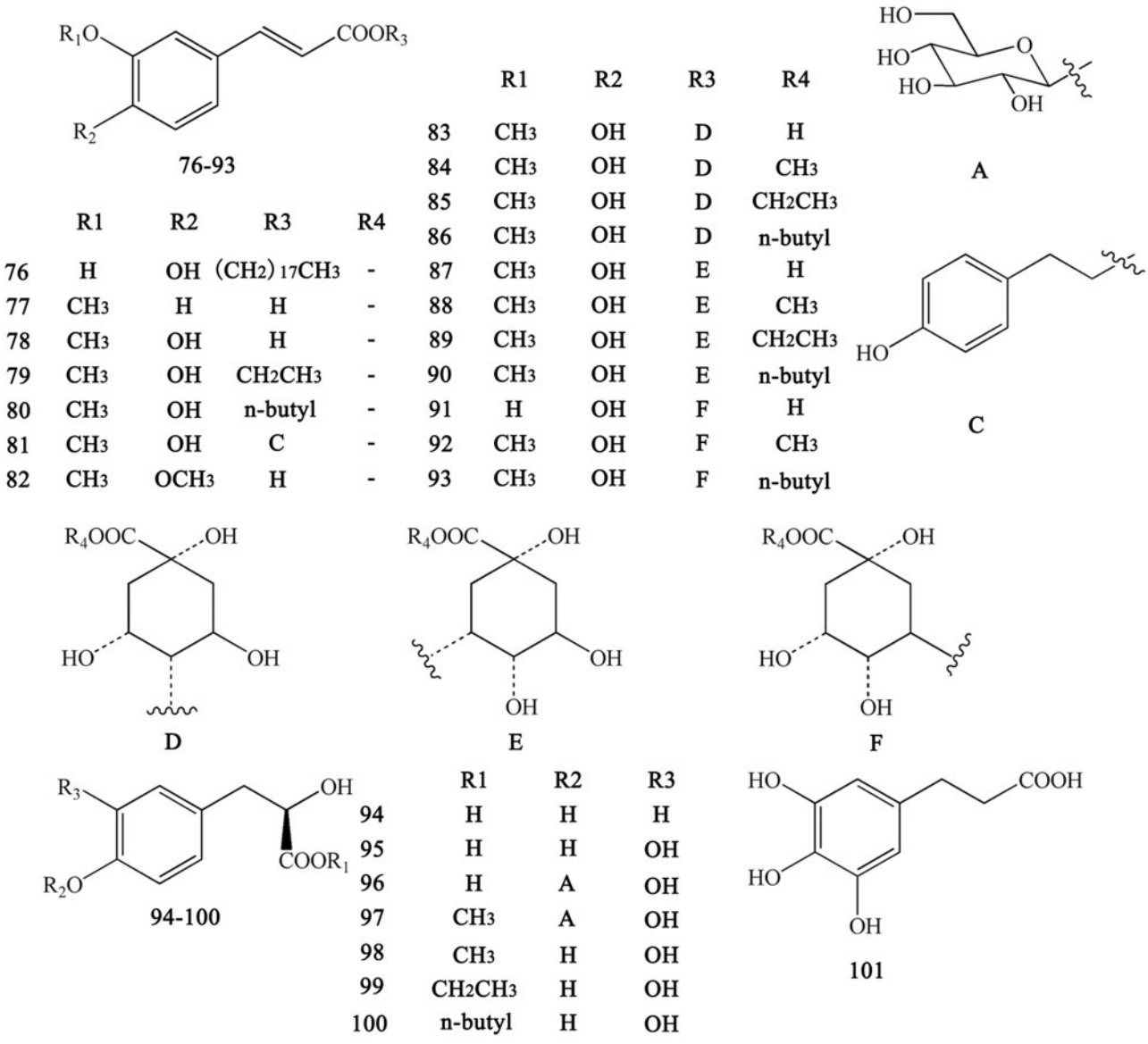


Figure 8. Simple phenylpropanoids in Coptidis Rhizoma.

4-*O*-feruloylquinic acid butyl ester (**86**), 5-*O*-feruloylquinic acid (**87**), methyl-5-*O*-feruloylquicinate (**88**), ethyl-5-*O*-feruloylquicinate (**89**), 5-*O*-feruloylquinic acid butyl ester (**90**), chlorogenic acid (**91**), methyl-3-*O*-feruloylquicinate (**92**), *N*-butyl-3-*O*-feruloylquicinate (**93**), 3-(4′-hydroxyphenyl)-(2*R*)-lactic acid (**94**), 3-(3′,4′-hydroxyphenyl)-(2*R*)-lactic acid (**95**), 3-(3′,4′-dihydroxyphenyl)-(2*R*)-lactic acid-4′-*O*-β-D-glucopyranoside (**96**), methyl-3-(4′-*O*-β-D-glucopyranosyl-3′,4′-dihydroxyphenyl)-lactate (**97**), methyl-3,4-dihydroxyphenyl lactate (**98**), ethyl-3,4-dihydroxyphenyl lactate (**99**), *N*-butyl-3,4-dihydroxyphenyl lactate (**100**), and 3-(2,3,4-trihydroxyphenyl) propanoic acid (**101**) (Figure 8).

Flavonoids

Previous research reported that CR also contains certain flavonoids, mainly including 6,8-dimethyl-3,5,7-trihydroxyfavone (**102**), rhamnetin (**103**), wogonin (**104**) (Meng et al. 2013), 7,4′-dihydroxy-5-methoxyfavanone (**105**), 2′,4,4′-trihydroxy-6′-methoxydihydrochalcone (**106**) (Min et al. 1987) , coptiside I (**107**), coptiside II (**108**) and woorenoside XII (**109**) (Fujiwara et al. 1976; Yoshikawa et al. 1997b) (Figure 9).

Other compounds

Other compounds isolated from CR include limonin (**110**), 3,4-dihydroxyphenylethyl alcohol (**111**), 3′,4′-dihydroxyphenethyl alcohol 1-*O*-β-D-glucopyranoside (**112**), 3,5-dihydroxyphenethyl alcohol-3-*O*-β-D-glucopyranoside (**113**), protocatechuic aldehyde (**114**), gentisic acid-5-*O*-β-D-glucopyranoside (**115**), apocynol (**116**), 1,2-dihydroxy-benzene (**117**), protocatechuic acid (**118**), vanillic acid (**119**), vanillic acid-4-*O*-β-D-glucopyranoside (**120**), protocatechuic acid methyl ester (**121**), protocatechuic acid ethyl ester (**122**), woorenoside VI (**123**), woorenoside VII (**124**), woorenoside VIII (**125**), woorenoside IX (**126**), cyclo-(Phe-Val) (**127**), cyclo-(Phe-Leu) (**128**), and β-sitosterol (**129**) (Yahara et al. 1985; Yoshikawa et al. 1997; Wang et al. 2007; Li XG et al. 2012; Li ZF et al. 2012; Ma H et al. 2013; Meng et al. 2013; Yang et al. 2014) (Figure 10).

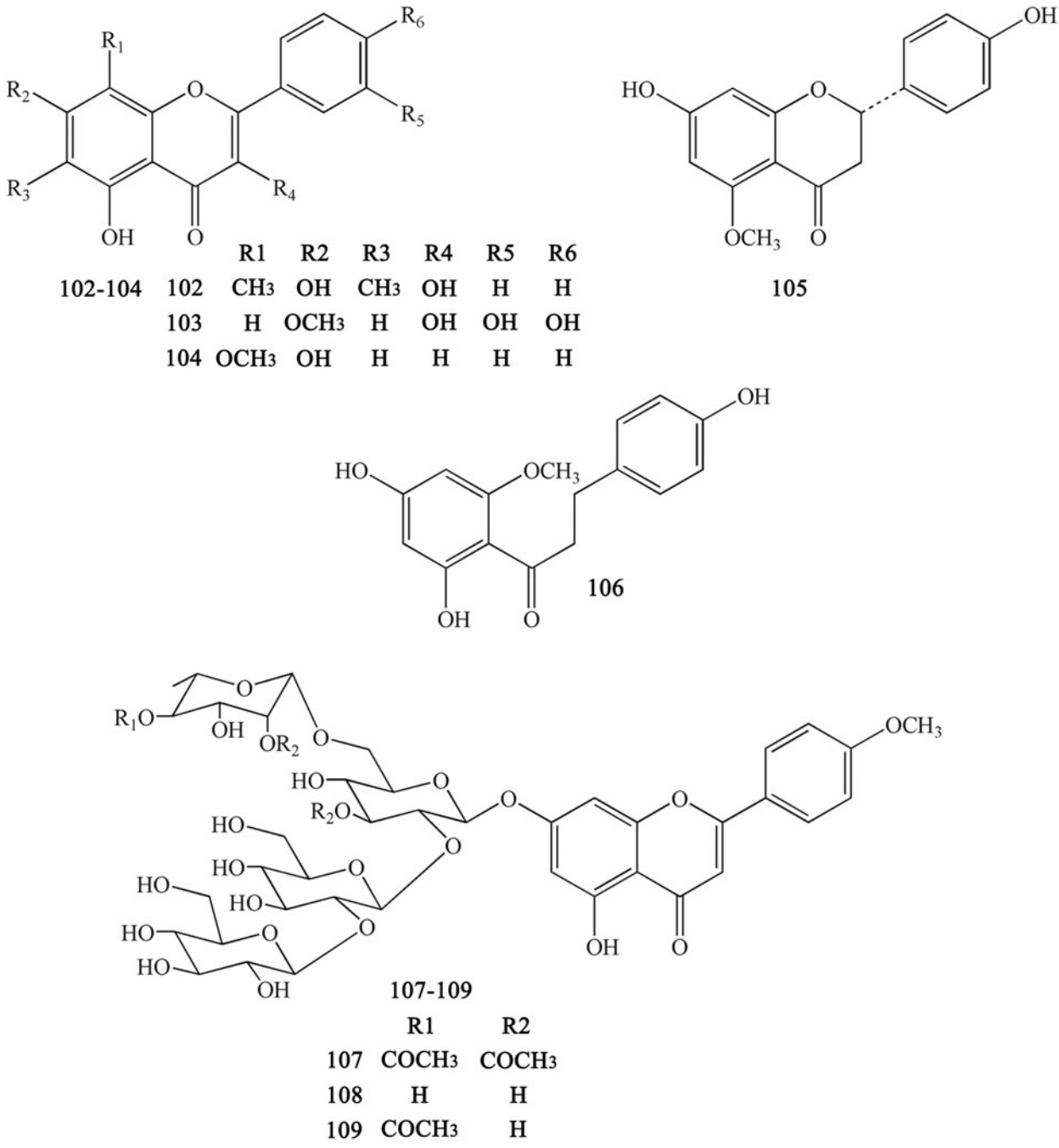


Figure 9. Flavonoids in Coptidis Rhizoma.

Pharmacology

Anti-pathogenic microorganism activity

Increasing research has been devoted to investigating the anti-pathogenic microorganism effects of CR, and its antibacterial, antiviral, and antifungal effects have been comprehensively studied and validated. Importantly, berberine has been recognized as the most important active monomer in this plant (Table 4).

Antibacterial effect

Berberine can inhibit Gram-positive (G^+) bacteria such as *Streptococcus agalactiae*, *Staphylococcus aureus*, *S.* mutans, *Bacillus anthracis*, *S. suis*, and *Enterococcus faecium* (Choi et al. 2007; Fan et al. 2008; Wang et al. 2014; Peng et al. 2015); and Gram-negative (G^-) bacteria such as *Actinobacillus pleuropneumoniae* (Kang et al. 2015), *Shigella dysenteriae* (Kong et al. 2010), and *Escherichia coli* (Boberek et al. 2010). Interestingly, alkaloids isolated from CR, especially epiberberine, can act as urease inhibitors to treat *Helicobacter pylori* infection (Tan et al. 2017). In 2014, Chen et al. reported that CR extracts (CRE) significantly inhibited *Salmonella typhimurium* with a minimum bactericidal concentration (MBC) of 12.5 mg/mL. Another study reported that although CRE had no effect on bacteria such as *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Proteus vulgaris*, after processing with ginger, it showed a marked inhibitory effect against these bacteria, especially *P. aeruginosa* (Li 2015).

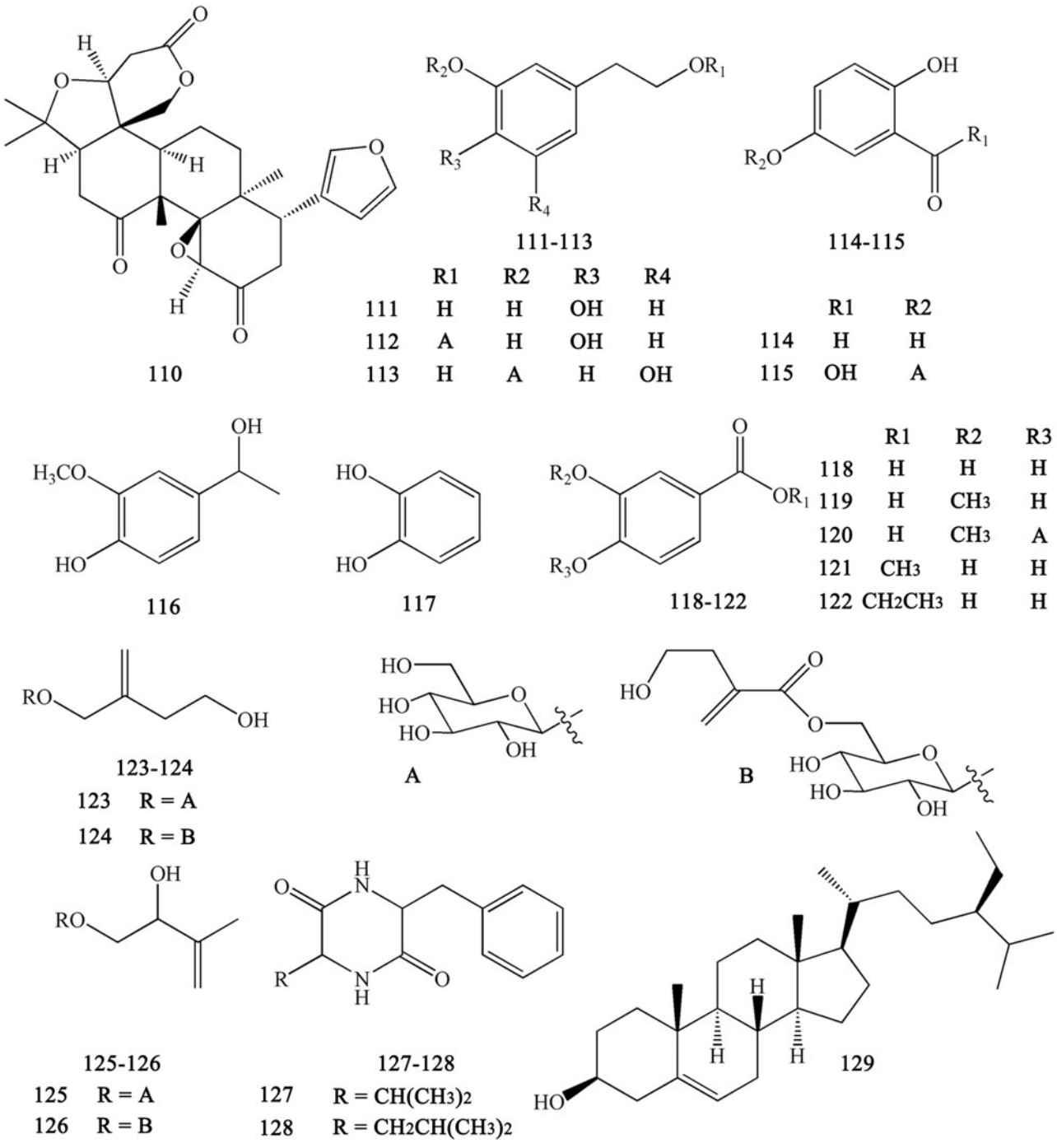


Figure 10. Other compounds in Coptidis Rhizoma.

Previous studies revealed that the antibacterial effects of CR and its active constituents were attributed to damaging the cell membrane, inhibiting protein and DNA synthesis, blocking bacterial division and development, and disturbing the formation of the Z-rings to inhibit the cell division protein FtsZ (Chu et al. 2014; Xue D et al. 2015; Ming et al. 2016). The antibacterial effect of CR alkaloids against G^+ bacteria was stronger than that against G^- bacteria, which could be explained by different the cell membrane structures of the pathogens (Yong et al. 2007). Kong W et al. (2009) performed a comprehensive analysis including the growth rate constant k, maximum power output of the log phase $P_{m,log}$, total heat output of the log phase $Q_{t,log}$, generation time t_g, growth inhibitory ratio I, and half-inhibitory concentration of the drugs (IC_{50}), and revealed that the antibacterial activities against *E. coli* of the four alkaloids from CR were in the order of berberine > coptisine > palmatine≫ jatrorrhizine.

Antiviral effect

Previous investigations revealed that CR and berberine have inhibitory effects against respiratory syncytial virus, influenza virus, enterovirus 71, herpes simplex virus, coronavirus and cytomegalovirus. In addition, studies showed that the inhibitory effects of berberine were mediated by downregulating cellular

Table 4. Anti-pathogenic microorganism effect.

Pathogenic microorganism	Extract/ compounds (number)	*In vivo*/ *In vitro*	Mechanism	Minimal active concentration/dose	Reference
Streptococcus agalactiae	1	*in vitro*	Damaging the structure of bacterial cell membrane and inhibiting synthesis of protein and DNA	MIC = 231.9 μM	(Peng et al. 2015)
Actinobacillus pleuropneumoniae	1	*in vitro*	Restraining DNA and protein syntheses, inhibiting the cleavage of bacteria, blocking the division and development of bacteria	MIC = 929.1 μM	(Kang et al. 2015)
Staphylococcus aureus	CRE	*in vitro*	Not mentioned	MIC = 77.8 μg/mL	(Feng et al. 2011)
Coagulase-negative *Staphylococcus strains*	1	*in vitro*	Not mentioned	MIC = 47.6 – 1522.2 μM	(Wojtyczka et al. 2014)
Shigella dysenteriae	1	*in vitro*	Not mentioned	MIC = 74.3 μM	(Kong et al. 2010)
Escherichia coli	1	*in vitro*	Heavily perturbing the formation of the Z-rings, inhibiting the cell division protein FtsZ	MIC = 1.5-4.5 mM	(Boberek et al. 2010)
Salmonella typhimuriummice	1	*in vivo*	As a LPS antagonist and blocking the LPS/TLR4 signaling	0.20 g/kg (mice), 0.05 g/kg (rabbit)	(Chu et al. 2014)
Helicobacter pylori	5	*in vitro*	Binding to the active-site sulfydryl groups	IC_{50} = 3.0 μM for HPU and 2.3 μM for JBU	(Tan et al. 2017)
Helicobacter pylori	1	*in vitro*	Not mentioned	74.3-743.2 μM	(Song et al. 2014)
Salmonella Typhimurium	CRE	*in vitro*	Regulation of the immune response	MBC = 12.5 mg/mLfor *S. Typhimurium* MBC = 25 mg/mL forST21	(Chang et al. 2014)
Aeromonas hydrophila	Total alklaoids	*in vitro*	Injuring membrane by increasing membrane lipid fluidity and changing conformation of membrane proteins, and reducing the secretion of virulence factors	MIC = 62.5 mg/L	(Xue D et al. 2015)
	1			MIC = 371.6 μM	
Staphylococcus aureus	1	*in vitro*	Not mentioned	IC_{50} = 169.5 μM	(Fan et al. 2008)
	3			IC_{50} = 209.2 μM	
	4			IC_{50} = 337.7 μM	
	5			IC_{50} = 636.2 μM	
	8			IC_{50} = 803.8 μM	
Herpes simplex virus	1	*in vitro*	Downregulation of JNK and NF-kappa B Activation	EC_{50} = 6.77 μM for HSV-1 EC_{50} = 5.04 μM for HSV-2	(Song et al. 2014)
Influenza virus	1	*in vitro* and *in vivo*	Inhibiting the virus infection, repressing inflammatory substances release	*In vivo*: 5 mg/kg; *In vitro*: IC_{50} = 74 μM	(Wu et al. 2011)
Respiratory syncytial virus	berberine chloride	*in vitro*	Inhibition of RSV-mediated early p38 MAPK activation	25 μM or 100 μM	(Shin et al. 2015)
Chikungunya virus	1	*in vitro*	Predominantly targeting the ERK arm of MAPK signaling	EC_{50} = 4.5 μM in human embryonic kidney cells EC_{50} = 12.2 μM in human osteosarcoma cells EC_{50} = 35.3 μM in CRL-2522 cells	(Varghese et al. 2016b)
Enterovirus 71	1	*in vitro*	Downregulating autophagy and MEK/ERK signaling pathway	IC_{50} = 7.43-10.25 μM	(Wang HQ et al. 2017)
H1N1 neuraminidase (NA-1)	CRE	*in vitro*	Inhibiting H1N1 neuraminidase (NA-1)	IC_{50} = 96.1 μg/mL	(Zhou et al. 2017)
	4			IC_{50} = 50.5 μM	
	8			IC_{50} = 67 μM	
	5			IC_{50} = 99.9 μM	
	1			IC_{50} = 233.7μM	
	coptisine			IC_{50} = 326.5 μM	
Coronavirus	CRE	*in vitro*	Inhibition of RNA-dependent RNA polymerase or proteases, affecting virus assembly or release	EC_{50} = 2.0 mg/mL	(Kim et al. 2008)
Human cytomegalovirus (HCMV)	berberine chloride	*in vitro*	Interfering with intracellular events after virus penetration into the host cells and before viral DNA synthesis	IC_{50} = 0.68 μM	(Hayashi et al. 2007)
Candida albicans	1	*in vitro*	Impairment mitochondrial function, generation of ROS, targeting cell wall integrity pathway and also affecting HSF1	Not mentioned	(Dhamgaye et al. 2014)

c-Jun N-terminal protein kinase (JNK) and NF-kappa B activation (Hayashi et al. 2007), suppressing mitogen-activated protein kinase (MAPK) or MAPK/ERK kinase 1 (MEK)/extracellular signal-regulated kinase (ERK) signalling (Shin et al. 2015; Varghese et al. 2016). Furthermore, berberine could suppress the EV71-induced autophagy by activating the AKT protein and inhibiting the phosphorylation of JNK and phosphatidylinositol-4,5-bisphosphate 3-kinase III (PI3KIII) (Wang HQ et al. 2017). H1N1 infection could be also suppressed by a water extract of CR, during which the main alkaloids served as neuraminidase inhibitors, and among them, palmatine was the most effective, with an IC_{50} of 50.5 μM (Zhou et al. 2017). The specific inhibition of West Nile virus (WNV) NS2B-NS3 protease and viral propagation by palmatine, with an IC_{50} of 96 mM, was investigated. Palmatine was also effective against dengue virus and yellow fever virus (Jia et al. 2010).

Antifungal effect

Berberine showed a weak inhibitory effect on *C. albicans* when used alone; while combined with fluconazole, the MIC value decreased sharply to 14.27 μM (Iwazaki et al. 2010). Other research showed that the antifungal effect of berberine was based on its ability to impair mitochondrial function, the generation of reactive oxygen species (ROS), targeting the cell wall integrity pathway, and affecting heat shock transcription factor 1 (HSF1) (Dhamgaye et al. 2014).

Protective effects on the cardiovascular system

Cardiovascular diseases (CVDs) involving the heart or blood vessels are the leading cause of death in worldwide. It is estimated that by 2030, over 23 million people will die from CVDs each year (Mendis et al. 2011). Importantly, CR can exert significant beneficial effects on major risk factors of CVDs, including anti-atherosclerotic, antihyperlipidemic, antidiabetic, antihepatic steatototic effects. Recent studies have shown that alkaloids in CR can protect against CVDs, such as coronary heart diseases, myocardial ischemia-reperfusion injury, heart failure, arrhythmia, and hypertension (Feng 2008; Mei 2011; Yong et al. 2011) (Table 5).

Anti-atherosclerotic effect

Atherosclerosis (AS) commonly occurs in the subendothelial space (intima) of arteries and is triggered by endothelial dysfunction and subendothelial lipoprotein retention (Tabas et al. 2015). It has been reported that CR and its main alkaloids, such as berberine and coptisine, could effectively prevent the development of AS, and the potential mechanisms are correlated with suppressing ROS mediated oxidation (Xu RX et al. 2017), and halting chronic inflammatory reactions via inhibition of intracellular inflammation signaling pathways (Feng et al. 2016, 2017). In particular, berberine could inhibit atherogenesis by reducing oxidative stress and the expression of adhesion molecules in the aorta, and increasing the levels of uncoupling protein 2 (UCP2) (Wang et al. 2011). Another CR component, magnoflorine, could inhibit the copper-mediated (Cu^{2+}) oxidation of various low-density lipoprotein (LDL) forms by increasing the lag time of conjugated diene formation and suppressing the generation of thiobarbituric acid reactive substances (TBARS) (Hung et al. 2007). The accumulation of foam cells in the subendothelial space is an indispensable step for the initiation and progression of AS. Berberine treatment could suppress foam cell formation, as well as the accumulation of lipid and cholesterol. The mechanism involves the activation of adenosine 5-monophosphate (AMP)-activated protein kinase (AMPK)-SIRT1-peroxisome proliferators-activated receptor γ2 (PPAR-γ) pathway and a decrease in ox-LDL uptake (Chi et al. 2014). Berberine can stabilize atherosclerotic plaques by inhibiting the expressions of matrix metalloproteinase 9 (MMP-9) and extracellular matrix metalloproteinase inducer (EMMPRIN) by suppressing activation of the p38 pathway (Huang et al. 2011).

Anti-hyperlipidemic effect

Hyperlipidemia, characterized by increased levels of blood lipids, has been implicated as a contributing factor to the development of cardiovascular diseases. The main mechanism of resisting hyperlipidemia is related to inhibiting lipogenesis and promoting the use, conversion and excretion of lipid (Iii et al. 2014). Alkaloids derived from CR, including berberine, coptisine, palmatine, epiberberine and jatrorrhizine, appeared to prevent body weight gain, reduce serum levels of total cholesterol (TC), triglyceride (TG) and low-density lipoprotein–cholesterol (LDL-c) and increase high-density lipoprotein–cholesterol (HDL-c) and promoted the excretion of total bile acids (TBA) in faeces (He et al. 2016; Yang W et al. 2016). The effect of berberine is mainly related to upregulating the LDL receptor (LDLR) and Cytochrome P450 7A1 (CYP7A1), while downregulating 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) (Ma et al. 2016). In addition, palmatine and epibeberine, which could also be beneficial to treat hyperlipidaemia and downregulate apical sodium dependent bile acid transporter (ASBT) (Zou et al. 2016; He et al. 2017). The sterol regulatory element-binding proteins (SREBPs) are transcription factors that regulate cholesterol by binding to the promoters of genes such as those encoding LDLR and HMG-CoA synthase. Interestingly, administration of coptisine, berberine and palmatine could activate SREBP2 (Kai et al. 2016). Besides these main alkaloids of CR, some minor alkaloids, such as berbamine, could also exert effects on hypercholesterolemic zebrafish by upregulating cholesterol transport and bile acid synthesis (Han et al. 2017).

Anti-obesity

Obesity is a pathological condition characterized by excessive body fat that often leads to cardiovascular diseases (Ashraf and Baweja 2013). 3T3-L1 cells are commonly used to detect fat metabolism. Previous studies revealed that five CR alkaloids (berberine, coptisine, palmatine, epiberberine and magnoflorine) could inhibit adipocyte differentiation and cellular triglyceride accumulation in 3T3-L1 cells, and downregulated adipocyte marker genes [including PPAR-γ and CCAAT/enhancer binding protein (C/EBP)] (Choi et al. 2014, 2015; Zhang et al. 2015). Lipolysis is the process of breaking down lipids and has been regarded as a target for treating obesity. Adiponectin, which is involved in the regulation of metabolic processes, binds to two main receptors (AdipoR1 and AdipoR2), whose expression levels are decreased during the development of obesity. Berberine treatment upregulated the expression of AdipoR1 and AdipoR2, which consequently elevated adiponectin production and induced lipolysis. Berberine could also directly upregulate lipolysis-related genes such as those encoding LPL, PPARα, carnitine

Table 5. Protecting cardiovascular system related diseases effect.

Pharmacological effects	Extract/compounds	Material or model	Mechanism	Dose	Reference
Lipid lowering effect	8	High fat (HF) diet C57BL/6J mice	Suppressing of lipogenesis and the enhancement of lipid oxidation in the liver	100 mg/kg, 56 d	(Yang et al. 2016)
Hypolipidemic Effect	3, 1, 8, 4, 5, Total alkaloids of CR (TACR)	High fat and high choesterol (HFHC) diet hamsters	Down-regulating the expression of HMGCR and up-regulating the expression of LDLR and CYP7A1 as well as promoting the excretion of TBA in the feces	46.7 mg/kg, for 140 d	(He et al. 2016)
Synergetic cholesterol-lowering effects of main alkaloids	3, 1, 8, 4, 5, TACR	HC diet hamsters; HepG2 cell	Up-regulating LDLR and CYP7A1, down-regulating HMGCR	*in vivo*: 70.05 mg/kg, 28 d; *in vitro*: 5 μg/mL	(Kou et al. 2016)
Antihyperlipidemia	4, 8, 1, 5,	Diabetic KK-Ay mice; HepG2 cell	not mentioned	*in vivo*: 225 mg/kg, 40 d; *in vitro*: 5 μg/mL	(Ma et al. 2016)
Antihypercholesterole	berbamine	HC diet adult zebrafish; zebrafish larvae; embryos	Up-regulating cholesterol transport and bile acid synthesis, inhibiting cholesterol synthesis and lipoprotein assembly or secretion	Adult: 2.25, 4.5 or 9 mg/fish, 28 d; Larvae: 10, 20 or 40 μg/mL, 10 d; embryo: 5, 10, 20, 40 or 80 μg/mL In vitro: 5, 10, 20, 40 or 80 μg/mL	(Han et al. 2017)
Antihyperlipidemia	3, 1, 4, TACR	HF diet C57BL/6J mice	Modulating of the enterohepatic circulation of bile acids and cross-talk between the gut microbiota and the liver	140 mg/kg, 35 d	(He et al. 2017)
Treating obesity	Ethanol extracts of CR, 1	HF diet C57BL/6J mice	Decreasing degradation of dietary polysaccharides, lowering potential calorie intake, activating mitochondrial energy metabolism, regulating on gut microbes	200 mg/kg, 42 d	(Xie W et al. 2011)
Treating obesity	1	High fat and high carbohydrate diet Wistar rats	Increasing the production of adiponectin and regulating the AMPK mechanism	380 mg/kg, 56 d	(Wu et al. 2016)
Anti-adipogenic activity	1, 3, 4, 5, 30	3T3-L1 cells	Downregulating C/EBP-α and PPAR-gamma	12.5-50 μM	(Choi et al. 2014)
Anti-adipogenic effect	5	3T3-L1 cells	Downregulating Raf/MEK1/ERK1/2 and AMPKα/Akt pathways during 3T3-L1 adipocyte differentiation	12.5, 25, 50 μM	(Choi et al. 2015)
Supressing adipocyte differentiation	1	3T3-L1 cells	Inhibiting cAMP/PKA-mediated CREB pathway	5 μM	(Zhang et al. 2015)
Treating atherosclerosis and other chronic inflammatory disease	3	ApoE(-/-) mice	Inhibiting activation of MAPK signaling pathways and NF-kappa B nuclear translocation	150 mg/kg, 84 d	(Feng et al. 2017)
Anti-atherosclerosis	1	Apolipoprotein E-deficient mice	Inhibiting oxidation and inflammation cytokine expressions	150 mg/kg, 84 d	(Feng et al.2016)
Suppressing atherogenesis	1	Western diet ApoE ($ApoE^{-/-}$) mice and $ApoE^{-/-}$/AMPK alpha $2^{-/-}$ mice; HUVECs	Suppressing atherogenesis via stimulation of AMPK-dependent UCP2 expression	*in vivo*: 1 mM in drinking water, 56 d; *in vitro*: 10 μM	(Wang et al. 2011)
Anti-atherogenic effect	1	THP-1-derived macrophages	Activating AMPK-SIRT1-PPAR-γ pathway and diminishing the uptake of ox-LDL	14.9, 29.7, 59.5 mg/L	(Chi et al. 2014)
Anti-atherogenesis	1	THP-1 cells	Suppressing the activation of p38 pathway	5, 10, 25, 50 μM	(Huang et al. 2011)
Against I/R injury	1	T2DM Wistar rats exposed to I/R	AMPK activation, AKT phosphorylation, and GSK3 inhibition in the nonischemic areas of the diabetic heart	100 mg/kg, 7 d	(Chang et al. 2016)
Alleviating cardiac I/R injury	1	I/R C57BL/6 mice, H9c2 myocytes,	Suppressing autophagy activation by decreasing the expression of SIRT1, BNIP3, and Beclin- p-AMPK and p-mTORC2 (Ser2481)	*in vivo*: 5 mg/kg, 10 mg/kg; *in vitro*: 5, 10, 20 μM	(Huang et al. 2015)
Anti- I/R injury	1	I/R SD rats	Attenuating mitochondrial dysfunction and myocardial apoptosis	200 mg/kg, 28 d	(Wang Y et al. 2015)
Anti-I/R injury	1	I/R SD rats, SIR H9c2 cells	Modulating Notch1/Hes1-PTEN/Akt signaling	*in vivo*: 200 mg/kg, 14 d; *in vitro*: 50 μM	(Yu et al. 2015)
Anti- I/R injury	1	I/R SD rats, SI/R H9c2 cells	Activating the JAK2/STAT3 signaling pathway and attenuating ER stress-induced apoptosis	*in vivo*: 200 mg/kg, 14 d; *in vitro*: 50 μM	(Zhao et al. 2016)

(*continued*)

Table 5. Continued.

Pharmacological effects	Extract/compounds	Material or model	Mechanism	Dose	Reference
Anti- I/R injury	1	I/R SD rats	Suppressing the activation of PI3K/AKT signaling,	100 mg/kg, 14 d	(Zhu and Li2016)
Anti-cardiac I/R injury	1	H/R H9c2 cells	Inhibiting apoptosis through the activation of Smad7	50 μM	(Yao et al. 2017)
Inhibition of autophagy induced by hypoxia	1	H9c2 cells under hypoxia	Inhibition of autophagy and suppression of AMPK activation	5, 10 or 25 μM	(Jia et al. 2017)
Attenuating MI/R injury	1	I/R SD rats, SI/R H9c2	Reducing oxidative damage and inflammation response, and SIRT1 signaling plays a key role	*in vivo*: 200 mg/kg, 14 d; *in vitro*: 50 μM	(Yu et al. 2016)
Anti- hypertrophy	1	High Glucose-and Insulin-Induced Cardiomyocyte	Activating the PPARα/NO signaling pathway	0.01-10 μM.	(Wang M et al. 2013)
Anti- acute myocardial ischemia	1	SD rats with isoproterenol	Anti-inflammatory and antioxidative activity through regulating HMGB1-TLR4 Axis	30, 60 mg/kg, 14 d	(Zhang T et al. 2014)
Anti-H/R damage	3	H/R H9c2 cell	Inhibition of autophagy	0.3, 1, 3, 10 μM	(Wang Y et al. 2017)
Anti-I/R injury	3	I/R SD rats	Suppressing myocardial apoptosis and inflammation by inhibiting the Rho/ROCK pathway	3, 10, and 30 mg/kg	(Guo et al. 2013)
Reducing I/R injury	4	I/R SD rats, HAEC cells, RAW 264.7 cells	Reducing oxidative stress and modulating inflammatory mediators	*in vivo*: 25, 50 mg/kg; *in vitro:* 1, 2, 5, 10 μM in HAEC; 1, 5, 10 μM in RAW 264.7 cells	(Kim et al. 2009)
Anti-nonalcoholic steatohepatitis	1	HF diet Balc/c mice	Normalizing gut microbiota, decreasing expression of endotoxin receptor, inflammatory cytokines	200 mg/kg, 56 d	(Cao et al. 2016)
Decreasing hepatic steatosis	1	HF C57BL/6J mice, H4IIE cells	Anti-inflammation	*in vivo*: 100 mg/kg, 28 d; *in vitro*: 10, 25, 50 μM	(Guo et al. 2016)
Attenuating hepatic steatosis	1	High fat and high-sucrose C57BL/6 mice, mouse primary hepatocytes, HepG2 cells	Inducing autophagy and fibroblast growth factor 21 in SIRT1-dependent manner	*in vivo:* 5 mg/kg, ip., 35 d; *in vitro*: 10 μM	(Sun et al. 2017)
Attenuating hepatic steatosis	1	HF diet SD rats, Huh7 cells	Global modulation of hepatic mRNA and lncRNA expression profiles	*in vivo:* 200 mg/kg, 112 d; *in vitro*: 10 μM	(Yuan et al. 2015)
Attenuating hepatic steatosis	1	Db/db mice and methionine-choline-deficient diet mice, tunicamycin-induced mice, HepG2 cells	Reducing endoplasmic reticulum stress through the ATF6/SREBP-1c pathway	*in vivo:* 200 mg/kg, 35 or 20 or 3 d respectively; *in vitro*: 5 μM	(Zhang et al. 2016)

palmitoyltransferase 1 (CPT1), and medium-chain acyl-CoA dehydrogenase (MCAD) (Wu et al. 2016).

Nonalcoholic fatty liver disease is a type of hepatic steatosis, which is always involved in obesity. It was reported that mice gut microbiota could be restored by gavage of 200 mg/kg of berberine for 8 weeks, resulting in alleviation of the predisposing factors for liver steatosis. These effects could be mediated by decreasing endotoxin receptor CD14 and inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumour necrosis factor alpha (TNF-α) (Cao et al. 2016). This finding is consistent with another study that suggested that berberine's actions are largely based on suppressing inflammation, independent of AMPK (Guo et al. 2016). Berberine could also attenuate hepatic steatosis and enhance energy expenditure in mice by inducing autophagy and fibroblast growth factor 21 (FGF21) expression; however, these effects were abolished by a deficiency of the nutrient sensor SIRT1 (Sun et al. 2017). Furthermore, increasing evidence suggests that the mechanism may correlate with global modulation of hepatic mRNA and long noncoding RNA (lncRNA) expression profiles, reducing endoplasmic reticulum stress (ER) stress through the ATF6/SREBP-1c pathway (Yuan et al. 2015; Zhang et al. 2016).

Protective effect against ischaemic heart disease

Cardiac ischemia is characterized by the deficient supply of blood flow and energy generating nutrients to the myocardium (Steenbergen and Frangogiannis 2012). The most effective treatment for ischaemic heart disease (IHD) is to re-perfuse the heart. However, re-perfusion could lead to series of additional injuries, termed ischaemia reperfusion injury (IRI) (Wijck and Buurman 2002). CR and its active compounds could reduce apoptosis, excessive autophagy, and inflammatory response, regulate energy metabolism, improve mitochondrial function, as well as alleviate ER stress, all of which might combine to alleviate IRI.

Berberine treatment could improve myocardial infarction and injury to cardiomyocytes, as indicated by the decrease of creatine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), and cardiac troponin (cTnI); reducing oxidative stress by suppressing malondialdehyde (MDA) production; and promoting superoxide dismutase (SOD) (Liu XT et al. 2010; Zhang T et al. 2014; Wang Y et al. 2015). *In vivo* and *in vitro* experiments showed that berberine could reduce the myocardial infarct size, improve cardiac function; and suppress myocardial apoptosis, oxidative damage, and ER stress through activating the JAK2/STAT3 signalling pathway (Zhao et al. 2016). Activation of the AMPK signalling pathway and silent information regulator 1 (SIRT1) signalling might be involved in the anti-autophagy and anti-apoptosis effect of berberine (Yu et al. 2016; Jia et al. 2017).

In pressure-overload-induced cardiac hypertrophy, berberine inhibited the mTOR, p38, and ERK1/2 MAPK signaling pathways to enhance autophagy, consequently attenuating left ventricular remodeling and cardiomyocyte apoptosis (Li MH et al. 2014). However, excessive autophagy activity can also cause cell death, termed 'autophagic cell death', also known as type-II programed cell death (Li S et al. 2017). It has been reported that berberine could reduce excessive autophagy by suppressing autophagy-related proteins, such as LC3-II, SIRT1, BNIP3 and Beclin-1, thus protecting H9c2 cells from hypoxia/reoxygenization (HR)-induced cell death (Huang et al. 2015). In non-ischemic areas of diabetic animal hearts, berberine increased myocardial glucose uptake, glycolysis, and fatty acid oxidation (Chang et al. 2016). The observation that berberine could act as an M2 muscarinic agonist, which reduced the spontaneous contraction rate of cardiomyocytes in culture might contribute to our understanding of berberine's complex actions on the heart (Salehi and Filtz 2011).

Studies have shown the berberine could reduce the release of TNF-α, IL-6, IL-β and HMGB1 to attenuate ischemic heart injury. TLR4, which is activated by HMGB1, is also reduced by berberine (Zhang T et al. 2014). Preconditioning with berberine for 14 days before the induction of I/R significantly attenuated myocardial I/R injury, as manifested by a reduction in the incidence of ventricular arrhythmia and the amelioration of myocardial histological changes. These effects were associated with the suppression of the PI3K/AKT signalling pathway and subsequent reduction of the expression of related inflammatory cytokinesis in the serum and myocardial tissue (Zhu and Li 2016).

Berberine could inhibit high glucose and insulin-induced cardiomyocyte hypertrophy, accompanied by increasing nitric oxide synthase (NOS) activity and NO concentration, which elevated PPARα and eNOS (Wang M et al. 2013). Coptisine also has an effect against myocardial ischemia reperfusion (MI/R) injury by suppressing myocardial apoptosis and inflammation via inhibition of the Rho/ROCK pathway, and inhibiting autophagosome formation rather than induction of autolysosomes in autophagy events (Guo et al. 2013; Wang Y et al. 2017).

Maintenance of mitochondrial integrity is one of the critical aspects of protecting the myocardium (Calo et al. 2013). Berberine could improve mitochondrial dysfunction, as indicated by increasing mitochondrial membrane potential, mitochondrial complex activity and decreasing the release of cytochrome C from mitochondria (Wang Y et al. 2015).

Antidiabetes

Diabetes mellitus (DM) is a common chronic diseases characterized by disorders of glucose metabolism that seriously threaten human health and longevity (Shi and Hu 2014). As early as the Wei and Jin Dynasties, Ming Yi Bie Lu recorded the treatment of CR for Xiaoke, which has been proven to be DM. CR and its components exert anti-diabetic effects by improving glucose metabolism, insulin resistance (IR), pancreatic beta cells and modulating the gut microbiota (Table 6).

Improving glucose metabolism

The expression of the glucose transporter protein (GLUT) is a key factor in the intracellular transport of glucose and is closely linked to cellular energy metabolism (Huang 2013). A previous report revealed that after treatment with berberine, the glucose uptake in L929 fibroblast cells, a cell line that express only GLUT1, reached maximum stimulation. Moreover, significant activation was observed within 5 min and reached a maximum at 30 min, which was attributed to the acute activation of the transport activity of GLUT1 (Cok et al. 2011). The level of GLUT1 protein was increased in 3T3-L1 cells, which was stated to be associated with the activation of AMPK stimulation (Kim et al. 2007). The upregulation of GLUT4 expression and downregulation of Retinol-binding protein 4 (RBP4) are also involved in glucose uptake (Zhang et al. 2008). HepG2 and βTC3 cell lines were used to test glucose consumption and insulin release, respectively. The results showed that glucose consumption by HepG2 cells was increased from 32% to 60% by berberine, which was insulin independent but had no influence on insulin secretion (Xie et al. 2011). Another study showed the GnRH-

Table 6. Antidiabetes effect.

Pharmacological effects	Extract/ compounds	Material or mode	Mechanism	Dose	Reference
Antihyperglycemia	1, 3, 4, 5, 8	Diabetic KK-Ay Mice; HepG2 cells	Not mentioned	*in vivo*: 225 mg/kg, 40 d; *in vitro*: 5 μg/mL	(Ma et al. 2016)
Lowering glucose concentration	1	HepG2 cells and betaTC3 cells	insulin independent but has no effect on insulin secretion	5 to 200 μM	(Xie X et al. 2011)
Activating glucose uptake	1	3T3-L1 adipocytes	Activating GLUT1 through AMPK stimulation	1, 5 μM	(Kim et al. 2007)
Treating type 2 DM	1	HF diet C57BL/6J mice, NIT-1 cells	Inhibiting mouse insulin gene promoter through activation of AMPK and exerting beneficial effect on pancreatic β-cell	*in vivo*: 50 mg/kg, 70 d; *in vitro*: 0.01-10 μM	(Shen et al. 2012)
Against insulin resistance	1	HF-diet and STZ induced Wistar rats, KK-Ay mice, HepG2, Bel-7402, L6 cells	Through PKC–dependent up-regulation of insulin receptor expression	*in vivo*: 150, 300 mg/kg, 15 d, 200 mg/kg, 21 d; *in vitro:* 22.3 μM	(Kong WJ et al. 2009)
Antihyperglycemic	1	HF diet C57BL/6J mice, db/db mice, 3T3-L1 and L6 cells	Inhibiting PTP1B activity and mimicing insulin action	*in vivo:* 100 mg/kg, 14 d; *in vitro:* 1.25-100 μM	(Chen et al. 2010)
Increasing glucose uptake	1	Insulin-sensitive and insulin-resistant rat skeletal muscle cells	Improving tyrosine-phosphorylation of IRS-1 and the recruitment of p85 to IRS-1, PKC and PKB activity, inhibiting mTOR	14.8 μM	(Liu LZ et al. 2010)
Treating type 2 DM	1	Alloxan-induced Wistar rats	Hypoglycemic effect, modulating lipids metabolic effects and to scavenge free radical	100, 200 mg/kg, 21 d	(Tang et al. 2006)
Insulinotropic effect	1	Primary rat islets	Activating HNF4α and GK	1, 3, 10 and 30 μM	(Wang et al. 2008)
Treating T1DM	1	Nonobese diabetic (NOD) mice	Protcting pancreatic islets and serum lipids	50, 150, 500 mg/kg, 98 d	(Chueh & Lin 2011)
Protecting pancreatic islets	1	STZ-treated primary pancreatic islet cells	Down-regulating Bax/Bcl-2 gene expression ratio	1, 3, 5 μM	(Chueh & Lin 2012)
Treating T2DM	1	HF diet and STZ induced rats	Lowering RBP4 levels and up-regulating the expression of GLUT4 protein in tissues	380 mg/kg, 28 d	(Zhang et al. 2008)
Antidiabetic effects	1	SD rats, NCI-H716 cells	Promoting GLP-1 secretion and GLP-1 biosynthesis in PKC-dependent pathway	*in vivo*: 60, 120 mg/kg, 35 d; *in vitro*: 1, 10, 100 μM	(Yu Y et al. 2010)
Ameliorating insulin resistance	1	HepG2 cells	Improving insulin sensitivity via its anti-inflammatory activity	0.1, 1, 10 μM	(Lou et al. 2011)
Treating T2DM	1	RAW264.7 microphages	Attenuating inflammation by SIRT1	5 μM	(Chuanchong 2016)
Treating T2DM	1	STZ induced ddY mice	Antioxidative stress via down regulating GPx and up-regulating CuZn-SOD	200 mg/kg, 14 d	(Lao-Ong et al. 2012)
Treating T2DM	1	high-carbohydrate/high-fat diet Wistar rats	Antioxidation and up-regulating P-TEFb expression	75, 150, 300 mg/kg, 42 d	(Zhou and Zhou 2011)
Treating diabetic neuropathy	1	SH-SY5Y cells	As an Nrf2 activator	0.1-10 nM	(Hsu et al. 2013)
Hypoglycemic	1	STZ induced diabetic SD rats, Caco-2 cells	Suppressing disaccharidase activities and the mRNA expression of SI complex in PKA-dependent pathway	*in vivo*: 100, 200 mg/kg, 35 d; *in vitro*: 2, 10, 50 μM	(Liu L et al. 2010)
Moderating glucose metabolism	1	HF diet SD rats	Regulating the MAPK and GnRh-Glp-1 pathways in the ileum	120, 240 mg/kg, 56 d	(Zhang Q et al. 2014)

glucagon-like peptide-1 (GLP-1) and MAPK pathways in the intestines might be involved in the mechanisms of berberine to modulate glucose metabolism (Zhang Q et al. 2014).

Improving insulin resistance

Insulin resistance (IR) is a pathological condition in which cells fail to respond to the normal actions of the hormone insulin. IR increases the risk of developing pre-diabetes and type-2 DM. Treatment with berberine at 50 mg/kg/day for 2 weeks was effective against the features of IR syndrome, and could improve levels of IR parameters, such as body weight, hyperglycemia, hyperinsulinemia, hypercholesterolemia, and hypertriglyceridemia (Ye et al. 2016). Shen et al. (2012) revealed that berberine could decrease insulin levels in pancreatic islet β-cells *via* reversible the concentration-dependent inhibition of the *INS2* promoter. Increasing the expression of insulin receptor (INSR) is also regarded as a target of berberine to increase insulin sensitivity. This effect is related to a protein kinase C (PKC)-dependent activation of its promoter (Kong WJ et al. 2009). In some insulin-resistant patients with diabetes, there is a phenomenon of increased INSR dephosphorylation by protein tyrosine phosphatase 1B (PTP1B). Interestingly, berberine can suppress the activation of PTP1B to increase the phosphorylation of INSR (Chen et al. 2010). Insulin receptor substrate (IRS) is a key molecule that acts after the insulin receptor and mediates insulin

signalling. In insulin signalling, the levels of phosphorylated AKT and IRS were significantly increased by berberine in alloxan-induced diabetic mice (Xie X et al. 2011). In insulin-resistant cells, berberine improved insulin-induced tyrosine-phosphorylation of IRS-1 and the recruitment of p85 to IRS-1, which was related to the inhibition of mTOR (Liu LZ et al. 2010).

Improving pancreatic β cells and promoting the secretion of insulin

Some studies reported that berberine could promote the secretion of insulin by increasing GLP-1 release or by stimulating pancreatic cells (Wang et al. 2008; Yu Y et al. 2010). Intragastric administration of berberine restored the damage to pancreas tissues and reversed the decreased in the number of islets in rats with DM (Tang et al. 2006; Chueh and Lin 2011). Berberine significantly downregulated the ratio of BAX/BCL-2 to block streptozotocin (STZ)-induced apoptosis in mouse pancreatic islets (Chueh and Lin 2012). Berberine and CRE exerted similar protective effect on islet β cells by improving islet β cell proliferation and the protein level of PARP1 (Jiang et al. 2017). Inflammation and oxidation are closely associated with DM. After treatment with berberine, decrease levels of proinflammatory cytokines, such as TNF-α, IL-6, iNOS, MCP-1 and COX-2, were observed (Jeong et al. 2009; Lou et al. 2011), while IL-10 levels were elevated in diabetic animals, in related cells, and in patients (Sun 2017). The levels of AR, SOD, GSH-px and GSH increased, while MDA decreased, indicating that oxidation was inhibited (Zhou and Zhou 2011; Lao-Ong et al. 2012). Multiple cellular kinases, as well as signalling pathways (such as MAPKs, AMPK, Nrf2/HO, NF-κB, and Rho GTPase pathways) were verified to be pivotal for berberine's activity in reducing oxidative stress and inflammation to treat DM (Wang et al. 2009; Xie et al. 2013; Mo et al. 2014). However, some studies showed that berberine could decrease hyperglycaemia and improve impaired glucose tolerance but did not increase insulin release and synthesis (Yin et al. 2002; Chen et al. 2010). In addition to berberine, recent studies showed that polysaccharides in CR increased glucose uptake, recovered glucose tolerance, inhibited the formation of advanced glycation end products, and reduced oxidation (Jiang et al. 2015; Cui et al. 2016; Yang Y et al. 2016).

Modulating gut microbiota

In recent years, berberine has been demonstrated to treat DM by modulating the structure and diversity of gut microbiota, including enrichment of beneficial microbes and inhibition of harmful microbes (Liu L et al. 2010). The bioavailability of berberine is very low, and the absorption rate is only 5–10% in the intestinal tract. However, it can significantly reduce the activity of disaccharidase and α-glucosidase in the intestinal tract, resulting in a reduction the absorption of glucose and postprandial hyperglycemia (Liu L et al. 2010; Li ZQ et al. 2012). CR alkaloid treatment avoided a decline in the diversity of gut microbes in obese mice and favoured the maintenance of a stable and healthy bacterial community in high-fat high cholesterol (HFHC)-fed animals (Kai 2017). Berberine can lead to an increase in the abundance of probiotics such as *Blautia*, *Bacteroides*, *Bifidobacteria* and *Lactobacillus*, and a decrease in relative abundance of *Firmicutes* and *Bacteroides* in the intestinal tract of animals (Meng et al. 2016; Gu et al. 2017).

Another study showed that the berberine selectively enriched the propionic acid producing bacteria and intestinal barrier repair bacteria *Ackermansia*; a CR decoction promoted butyric acid producing bacteria, such as *Coprococcus*, *Faecalibacterium* and *Oscillospira*. Compared with berberine, the CR decoction induced higher flora diversity, and the flora structure was closer to that of normal animals (Ti 2017). The increase of GLP-1 and short-chain fatty acids in the gut may account for the structural and diversity changes to the microbiota induced by berberine (Sun et al. 2016).

Anticancer effect

Cancer is the second leading cause of death globally and was responsible for 8.8 million deaths in 2015. Globally, nearly 1 in 6 deaths are caused by cancer, as reported by the World Health Organization. Studies showed that CR and berberine are effective against multiple types of human cancer, including bladder, breast, cervix, cholangiocarcinoma, colon, Ehrlich, gastric, glioma, intestine, kidney, leukemia, liver, lung, nasopharyngeal, melanoma, myeloma, ovary, pancreas, prostate and sarcoma (Ho et al. 2009; Wang N et al. 2015). CR and its active ingredients can prevent cancer by blocking the cell cycle, inhibiting tumor cell proliferation, inducing apoptosis, inhibiting migration and invasion, and enhancing the body's immune function (Table 7).

Inducing apoptosis

Berberine induces apoptosis in human colonic carcinoma cell line SW620; in the pancreatic cancer cell lines PANC-1 and MIA-PaCa2; and in breast cancer MCF-7 cells through the generation of ROS. Moreover, berberine had a greater apoptotic effect in PANC-1 cells than gemcitabine (Hsu et al. 2007; Xie et al. 2012; Park et al. 2015). When compared with chemical drugs (meloxicam and rosiglitazone) and berberine, total alkaloids showed a greater apoptosis-inducing effect (Ke 2007). Various apoptotic modulating signals are involved the induction of apoptosis by berberine. Berberine could markedly inhibit the expression of survivin in MGC-803gastric cancer cells, in SKOV3ovarian cancer cells (Zhang et al. 2013; Ma et al. 2015); and activated caspase-3, caspase-8, caspase-7 and caspase-9 in FaDu head and neck squamous cell carcinoma cells and malignant pleural mesothelioma (Yao 2014; Seo et al. 2015). Berberine also regulated the activities of Bcl-2 and Bax in colon cancer cells (Chidambara et al. 2012), FoxO1 and FoxO3 in HepG2 cells (Shukla et al. 2014), and p53 in MCF-7 and MDA-MB231breast cancer cells (Kim et al. 2012). Additionally, cPLA-COX2 and JAK2/STAT3 signalling was inhibited in liver cancer cells and colon cancer cells HT-29 (Li O et al. 2013; Li C et al. 2014). Berberine also promoted the Fas/FasL signalling pathway, and then triggered the activation of caspase-8 and caspase-9 precursors to induce apoptosis in human oral cancer cells (Kim et al. 2015). In HCT-116 colon cancer cells, berberine enhanced GRP78 activity by binding to and forming complexes with GRP78, which increased the ability of GRP78 to bind to VPS34. This suggested berberine could induce autophagic cancer cell death (La et al. 2017). *In vitro* and *in vivo* experiments showed that coptisine inhibited the proliferation, growth and migration of HCC cells and colorectal cancer cells, and promoted their apoptosis. Other studies showed that coptisine activated microRNA miR-122 (Chai et al. 2018) and the 67-kDa Laminin Receptor (Zhou et al. 2018), and inhibited MFG-E8 (Cao et al. 2018).

Table 7. Anticancer effect.

Pharmacological effects	Extract or compounds	Material or model	Mechanism	Dose	Reference
Treating melanoma	1	A375 cells	Up-regulating p38 MAPK, GR and down-regulating DHODH	5, 10, 20, 40, 80 μM	(Liu B et al. 2017)
Treating melanoma	1	B16 cells	Modulating the PI3K/Akt pathway, RARα/RARβ expression	10, 20, 40 μM	(Kou et al. 2016)
Treating hepatocellular carcinoma	1	HepG2 cells	Promoting apoptosis through the NF-κB p65 pathway	10, 50, 100 μM	(Li M et al. 2017)
Treating hepatocellular carcinoma	CRE	HepG2 cells, MHCC97-L and HepG2 cells xenograft mice	Suppressing vascular endothelial growth factor via inactivation of eukaryotic elongation factor 2	*in vitro:* IC_{50} of 500 and 150 μg/mL at 24 and 48 h in MHCC97L cells, 250 and 120 μg/mL in HepG2 cells; *in vivo*: 50 mg/kg/2 d, 21 d	(Tan et al. 2014)
Treating hepatocellular carcinoma	CRE	MHCC97-L cells	Downregulating the Rho/ROCK signaling pathway	300, 150 μM at 24 h and 48 h	(Wang N et al. 2010)
Treating hepatocellular carcinoma	1	HepG2 and MHCC97-L cells	Increasing Bax expression, activating Beclin-1, inhibiting mTOR-signaling pathway by suppressing the activity of Akt and up-regulating P38 MAPK signaling	IC_{50}: 100 μM in HepG2 cells, 250 μM in MHCC97-L cells	
Treating hepatocellular carcinoma	berberine hydrochloride	HepG2 cells	AMPK activation	50, 100 μM	(Yu et al. 2014)
Treating hepatocellular carcinoma	3	SMMC7721 xenograft mice, SMMC7721 and HepG2 cells	Induction of apoptosis through a 67LR/cGMP pathway	*in vivo*: 50 mg/kg; *in vitro*: 12.5, 25, 50,100 μM;	(Zhang et al. 2018)
Treating glioma	Coptis Chinensis granules	Xenograft mice, U87 cells	Down-regulating phosphorylation of STAT3 by reducing HDAC3	*in vivo*: 20, 10 mg/per mouse, 1 month at intervals of 1 d; *in vitro*: 0.625, 1.25, 2.5, 5 or 10 mg/mL;	(La et al. 2017)
Inducing autophagic cell death	1	HCT-116, HepG2, DLD1cells	enhancing GRP78 levels and The ability of GRP78 to bind to VPS34	IC_{50}: 80, 100, 200 μM in HCT-116, HepG2, DLD1 respectively	
Treating osteosarcoma	1	Xenograft mice, Saos-2 and MG-63 cells	Downregulating caspase-1/IL-1β inflammatory signaling	*in vivo*: 20 mg/kg, 21 d; *in vitro*: 50 μM	(Jin et al. 2016)
Treating osteosarcoma	1	MG-63 cells	Inducing apoptosis and DNA damage	20, 40, 60, 80 μM	(Zhu et al. 2014)
Treating osteosarcoma	3	xenografted mice; MG63, SW1353, Saos-2, and U-2OS cells	Downregulating the expression of CDK4, cyclin D1, VE-cadherin and integrin ß3, diminishing STAT3 phosphorylation	*in vivo*: 50 mg/kg, 24 d; *in vitro:* IC_{50}: 12.99 ± 0.77, 14.10 ± 2.17, 22.56 ± 2.94, and 28.54 ± 5.71 μM, respectively	(Yu D et al. 2014)
Treating esophageal cancer	1	KYSE-30 cells	Anti-migration and anti-metastasis mediated by chemokine receptors	IC_{50}: 60, 45 and 40 μM after 24, 48 and 72 h, respectively	(Mishan et al. 2015)
Treating lung cancer	1	H460, H1975 cells	Suppressing both phosphorylated and total levels of STAT3 protein and promoting STAT3 degradation by enhancing ubiquitination	IC_{50}: 13.4 and 62.43 μM for H460 and H1975 cells	(Zhu et al. 2015)
Treating human gastric cancer	1	xenograft nude mice, BGC-823 and SGC7901 cells;	Ihibiting the Akt/mTOR/p70S6/S6 pathway	*in vivo:* 10 mg/kg injected intratumorally once every 3 d for 18 d *in vitro:* 10, 25, 50, 75, 100 μM	(Yi et al. 2015)
Treating breast cancer	3	MDA-MB-231 cells	Anti-metastatic function through down-regulation of MMP-9 in combination with the increase of TIMP-1	16, 32, 64 μM	(Li J et al. 2014)
Treating nasopharyngeal carcinoma	berberine hydrochloride	CNE-1 cells	Blocking proliferation, migration and invasion, inducing apoptosis	IC_{50}: 31.5 μM	(Li CH et al. 2014)
Treating tongue squamous cancer	1	SCC-4 cells	Inhibiting FAK, IKK, NF-kappaB, u-PA and MMP-2 and -9	62.5, 125 μM	(Ho et al. 2009)
Treating human colon cancer	1	SW620 cells		50 μM	(Hsu et al. 2007)

(*continued*)

Table 7. Continued.

Pharmacological effects	Extract or compounds	Material or model	Mechanism	Dose	Reference
			Generating reactive oxygen species and activation of JNK/p38 MAPK and FasL		
Treating colorectal cancer	3	Xenograft mice; HCT116 cells	Inhibiting epithelial–mesenchymal transition, the growth, adhesion and metastasis, down-regulating MFG-E8	*in vivo*: 30, 60, 90 mg/mL, 14 d; *in vitro*: 62.4, 124.8, 249.6 μM;	(Cao et al. 2018)
Treating pancreatic cancer	4	PSC cells, HPNE, MIA PaCa-2, CFPaC-1 and PANC-1 cells	Inhibiting glutamine-mediated PSC-PCC interaction through simultaneous inhibition of survivin and COL1A1	212.8, 425.6 μM	(Chakravarthy et al. 2018)
Treating esophageal cancer	Coptidis Rhizoma, 1	Xenograft mice, YES-2, YES-2 cells	Down-regulating tumor IL-6 production	*in vivo*: oral food supplement of final concentration of 1%; *in vitro*: 8-32 mM	(Iizuka et al. 2000)

Cell cycle arrest

Berberine inhibited the expression of Cyclin D1 and the activity of the related AP-1 and Wnt pathways. Berberine prevented the proliferation of lung cancer PG cells by inhibiting Cyclin D1, increasing the number of cells in the Go/G1 phase, and decreasing the number of cells in the S phase and G2/M phase (Ye 2007). Berberine blocked human gastric carcinoma cell entrance into the cell cycle in the G0/G1 phase, and inhibited colorectal adenocarcinoma growth by inducing G2/M phase arrest (Sha et al. 2011; Cai et al. 2014). However, CR and berberine decreased the number of CNZ-2Z cells in the Go/G1 phase significantly, while the number of cells in the S phase increased significantly, indicating that the cell cycle was blocked in the S phase (Cui et al. 2008). In osteosarcoma, berberine treatment led to G1/S cell cycle arrest in p53-presenting cells, but may cause G2/M arrest in p53-deficient cells, suggesting that p53 may play diverse roles in the cell cycle distribution in berberine-treated cancer cells (Liu et al. 2009). In addition, another CR component, jatrorrhizine, could inhibit the proliferation and neovascularization of C8161 human metastatic melanoma cells by inducing cell cycle arrest at the G0/G1 transition (Liu et al. 2013). Moreover, columbamine could suppress proliferation and neovascularization of metastatic osteosarcoma U2OS cells with low cytotoxicity and induced cell cycle arrest at the G2/M transition, which was associated with attenuation of CDK6 gene expression, STAT3 phosphorylation and MMP2 expression (Bao et al. 2012).

Inhibiting tumour metastasis

Urokinase-type plasminogen activator (uPA) and MMPs play important roles in cancer metastasis and angiogenesis, and inhibition of uPA and MMP could inhibit the migration and invasion of cancer cells. Berberine affected JNK, ERK1/2, p38 MAPK, P13K-Akt and NF-κB signalling pathways to inhibit the actions of MMP-2, MMP-9, MMP-1, and uPA in SCC-4 human tongue squamous carcinoma cells, hepatoma cells, and breast cancer cells (Ho et al. 2009; Bing et al. 2011; Kim et al. 2012; Kuo et al. 2012). NM23-H1 and SDF-1 are potential genes associated with tumour cell metastasis and previous research indicated that berberine could decrease NM23-H1 and SDF-1 expression; thus reducing the metastasis of leukaemia cells (Li, Guo, et al. 2008; Liu et al. 2008). It was reported that berberine (50 μM) could act as a RhoGTPases inhibitor in HONE1 human nasopharyngeal carcinoma cell (Tang et al. 2009). Inhibition of RhoGTPase by CRE, as well as by berberine (100-200 μM), might also result in blockade of ROCK signalling in hepatoma cells (Wang et al. 2010). The expression levels of two chemokine receptors (CXCR4 and CCR7), which are involved in the migration and metastasis of esophageal cancer cells, were decreased following the berberine treatment (Mishan et al. 2015).

Tumour angiogenesis, a process associated with invasion and metastasis, is an essential link in the control of tumour progression (Zhao and Adjei 2015). In tumour angiogenesis, VEGF and hypoxia-inducible factor-1α (H1F-1α) play a key role in tumour progression. *In vivo* and *in vitro* studies revealed that the antiangiogenic activity of berberine was mediated by downregulating the expression of H1F-1, VEGF and proinflammatory mediators in hepatocellular carcinoma cells and breast cancer cells (Jie et al. 2011; Hamsa & Kuttan 2012; Kim et al. 2013). Berberine may also inhibit the adhesion of gastric cancer cells to endothelial cells by increasing the proportion of intercellular adhesion

molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), thus reducing the risk of tumour angiogenesis induced by evodiamine (Shi et al. 2013). In addition, berberine showed anti-angiogenesis effects on animals that were orthotopically implanted with hepatocellular carcinoma (Tsang et al. 2015). Coptisine at 150 mg/kg may reduce cancer metastasis risk by inhibiting the RAS-ERK pathway in HCT116 bearing mice (Huang et al. 2017).

Chinese medicinal herbs can enhance the body's immune function, by inducing cytokines, interferon (IFN), lymphocyte-activated killer cells production and natural killer (NK) cell proliferation, thereby mediating tumor cell apoptosis. Importantly, CRE could markedly increase the IFN-β and TNF-α mRNA expression in breast cancer MCF-7 oestrogen receptor-positive cells (Kang et al. 2005) Furthermore, berberine was also capable of reducing the expression of caspase-1 and IL-1β in osteosarcoma cells, and inhibiting the growth of tumour cells, suggesting that the mechanism might involve downregulation of the caspase-1/IL-1β inflammatory signalling axis (Jin et al. 2016). A recent study showed that palmatine disrupted the interaction between pancreatic stellate cells and cancer cells in the tumour microenvironment, consequently resulting in the inhibition of cancer growth and migration, while inducing apoptosis by inhibiting survivin (Chakravarthy et al. 2018).

Other pharmacological effects

Experimental studies showed that CR and its compounds could be used to treat diseases of nervous system, digestive system, skeleton, and skin and hepatotoxicity, nephrotoxicity and aging-related disorders (Lee et al. 2010; Su et al. 2017). Berberine could ameliorate β-amyloid pathology, gliosis, and cognitive impairment in an Alzheimer's disease transgenic mouse model through the PI3K/AKT/GSK3 signalling pathway and induced 6-hydroxydopamine-induced human dopaminergic neuronal cell death through the induction of heme-oxygenase-1 and exert antidepressant action through inhibition of organic cation transporter 2 and 3 (Durairajan et al. 2012; Bae et al. 2013; Sun et al. 2014). Furthermore, CR could treat Alzheimer's disease via the significant inhibition of acetylcholinesterase (AchE) (Kaufmann et al. 2016). CRE, coptisine and jatrorrhizine displayed neuroprotective effect by alleviating oxidative stress (Friedemann et al. 2015, 2016; Luo et al. 2016). Berberine prevented glucocorticoid-induced bone loss in lumbar spongy bone by promoting bone formation and inhibiting bone resorption (Bilian et al. 2011). CRE had a radioprotective effect against radiation-induced skin damage in rats by modulating oxidative stress in skin and in aging-related diseases via antioxidation and AMPK activation (Wang XJ et al. 2013; Xu Z et al. 2017). In the digestive system, CR extracts could exert an analgesic effect on a rat model of irritable bowel syndrome by decreasing serotonin release and cholecystokinin expression (Tjong et al. 2011). Coptisine showed a significant gastric mucosal protective effect on stress gastric ulcers in mice. However, the protective effect of coptisine (57 mg/kg) on the gastric mucosa was significantly better than that of 100 mg/kg berberine (Feng et al. 2007). Jatrorrhizine delayed gastric emptying and intestinal transit in postoperative ileus (Zhang et al. 2012). Berberine has the potential to alleviate premenopausal syndrome by decreasing oxidative stress, LDL, triglycerides, insulin resistance and improving mood (Caliceti et al. 2015).

Pharmacokinetics

Currently, pharmacokinetics research on CR has mainly focused on the protoberberine alkaloids. After oral intake, blood exposure and absolute bioavailability are extremely low. During absorption, 50% of berberine undergoes extensive first-pass elimination (Liu Y et al. 2010). Then, the absorbed alkaloids are quickly and widely distributed in tissues, such as the brain, intestine, stomach, pancreas, heart, kidney, liver, spleen, lung, testicles and uterus, among which the liver has the highest concentration (Ma et al. 2010). Furthermore, the concentrations of the alkaloids in tissues are not only higher than those in circulation, but also are eliminated at a slower rate (Liu Y et al. 2010). Researchers have analysed metabolites from urine, feces, plasma, and intestinal flora and found that they mainly comprise the sulphate and glucuronide conjugates of the CR alkaloids or the Phase I metabolites of the alkaloids (Yang et al. 2010). In liver microsomes, cytochrome P450 isoenzymes (CYPs) play a major role. The intestinal flora also exerts significant effect on the enterohepatic circulation of the metabolites, which may be related to the multiple peaks phenomenon of the pharmacokinetics of the CR alkaloids (Zuo et al. 2006). Berberine is usually excreted in urine and bile. Other studies showed, only 0.013% of berberine is eliminated directly in urine after oral administration (Yu et al. 2000). The metabolites are mainly eliminated via urine (Yang et al. 2010), and aproportion of them are also eliminated through bile (Zuo et al. 2006). However, in some pathological conditions, such as diabetes mellitus, PI-IBS (post-inflammation irritable bowel syndrome) and lipopolysaccharide-related diseases, the pharmacokinetic processes are altered. In 2008, Yu et al. showed a higher exposure of berberine, palmatine, coptisine, epiberberine and jatrorrhizine, with 170–330% increases in C_{max} (maximum concentration) and 150–350% increases in $AUC_{0\text{-}24}$ (area under curve) in diabetic rats, after oral administration of CRE (1.3 g/kg). Then, in 2010, they discovered that impairment of the function and expression of P-glycoprotein in the intestine partly contributed to the increased exposure of the five protoberberine alkaloids (Yu et al. 2010).

After oral intake of berberine, the $AUC_{0\text{-}t}$ in mice with PI-IBS was higher than that in normal mice, while the total body clearance decreased significantly (Gong et al. 2014). In a pharmacokinetic study, magnoflorine showed lower bioavailability and faster absorption and elimination. However, pharmacokinetic parameters altered remarkably when magnoflorine was administered in a CR decoction. Oral gavage of a CR decoction decreased the absorption and elimination rates of magnoflorine, which revealed the pharmacokinetic interactions between magnoflorine and the rest of ingredients in CR (Xue B et al. 2015). Berberine in plasma was quickly eliminated after intravenous injection of CR; however, berberine could penetrate the blood-brain barrier (BBB) and reached the hippocampus with a rapid increase and slow elimination (Wang et al. 2005; Table 8).

Toxicology

CR has been banned in Singapore in recent decades because of the suggestion that berberine aggravated jaundice and kernicterus in neonates with glucose-6-phosphate dehydrogenase deficiency (Wong 1980). In 2012, researchers found no organ toxicity or electrolyte imbalance in 20 patients administered with CR at a daily dose of 3 g for 1055 patient-days (Linn et al. 2012). In 2016, the ban of Chinese herbal medicines rich in berberine was officially lifted. Nevertheless, toxicity cannot be ignored. An

Table 8. The pharmacokinetic parameters of component in animals and humans.

Subjects/animals	Drug administered	Dosages	Detected compounds	Pharmacokinetic parameters	References
Male SD rats	TACR (i.g.)	1.3 g/kg	1	AUC_{0-24} (ng·h·mL^{-1}): 147.66 ± 14.19, C_{max} (ng·mL^{-1}): 11.39 ± 1.62, T_{max} (h): 3.40 ± 1.47, MRT (h): 9.31 ± 0.81	(Yu et al. 2007)
			3	AUC_{0-24} (ng·h/mL): 11.74 ± 7.24, C_{max} (ng/mL): 1.52 ± 0.74, T_{max} (h): 2.25 ± 1.82, MRT (h): 6.69 ± 2.07	
			5	AUC_{0-24} (ng·h/mL): 10.19 ± 6.67, C_{max} (ng/mL): 2.40 ± 0.88, T_{max} (h): 1.30 ± 1.56, MRT (h): 5.09 ± 2.44	
			8	C_{max} (ng/mL): 0.84 ± 0.47, T_{max} (h): 1.69 ± 1.72	
			4	AUC_{0-24} (ng·h/mL): 14.80 ± 2.25, C_{max} (ng/mL): 1.74 ± 0.56, T_{max} (h): 0.90 ± 0.95, MRT (h): 10.12 ± 1.16	
Male diabetic SD rats	CRE (i.g.)	1.3 g/kg	1	AUC_{0-24} (ng·h/mL): 255.10 ± 8.04 C_{max} (ng/mL): 24.97 ± 8.39 T_{max} (h): 3.10 ± 1.52 MRT (h): 9.44 ± 1.52	(Yu et al. 2008)
			3	AUC_{0-24} (ng·h/mL): 35.53 ± 10.32 C_{max} (ng/mL): 4.88 ± 1.40 T_{max} (h): 2.80 ± 1.44 MRT (h): 8.17 ± 1.30	
			5	AUC_{0-24} (ng·h/mL): 35.97 ± 11.14 C_{max} (ng/mL): 6.26 ± 2.37 T_{max} (h): 2.80 ± 1.44 MRT (h): 7.28 ± 1.71	
			8	AUC_{0-24} (ng·h/mL): 8.17 ± 3.30 C_{max} (ng/mL): 1.30 ± 0.23 T_{max} (h): 3.00 ± 1.06 MRT (h): 6.84 ± 1.45	
			4	AUC_{0-24} (ng·h/mL): 22.02 ± 4.39 C_{max} (ng/mL): 2.93 ± 1.14 T_{max} (h): 4.00 ± 3.79 MRT (h): 9.30 ± 0.61	
Male pseudo germ-free Wistar rats	1 (i.g.)	40 mg/kg	1	$AUC_{0\text{-}limt}$ (ng·h/mL): 40.89 MTT (h): 10.25	(Zuo et al. 2006)
			Berberrubie,	$AUC_{0\text{-}limt}$ (ng·h/mL): 437.29, MTT (h): 7.45	
			Thalifendine	$AUC_{0\text{-}limt}$ (ng·h/mL): 287.85 MTT (h): 4.84	
			Emethylen-eberberine	$AUC_{0\text{-}limt}$ (ng·h/mL): 735.22 MTT (h): 15.08	
			8	$AUC_{0\text{-}limt}$ (ng·h/mL): 101.98 MTT (h): 4.05	
Male Wistar rats	1 (i.g.)	40 mg/kg	1	$AUC_{0\text{-}limt}$ (ng·h/mL): 37.42, MTT (h): 10.53	
			Berberrubie	AUC_{0limt} (ng·h/mL): 1879.64, MTT (h): 18.32	
			Thalifendine	$AUC_{0\text{-}limt}$ (ng·h/mL): 811.05, MTT (h): 7.62	
			Emethylen-eberberine	$AUC_{0\text{-}limt}$ (ng·h/mL): 1763.62, MTT (h): 24.68	
			8	$AUC_{0\text{-}limt}$ (ng·h/mL): 356.05, MTT (h): 10.32	
Post inflammation irritable bowel syndrome male Wistar rats	berberine hydrochloride (i.g.)	25 mg/kg	1	$AUC_{0\text{-}t}$ (ng·min/mL): 2,763.43 ± 203.14 C_{max} (ng/mL): 18.53 ± 0.61 T_{max} (min): 15.00 ± 0.00 $T_{1/2,\lambda z}$ (min): 941.45 ± 60.39 $V_d/F_{\lambda z}$ (L/kg): 41,202.89 ± 4,112.68 CL/F (L/h/kg): 3,270.57 ± 58.32	(Gong et al. 2014)
Male SD rats	berberine hydrochloride (i.g.)	25 mg/kg	1	$AUC_{0\text{-}t}$ (ng·min/mL): 2,039.49 ± 492.24C_{max} (ng·mL^{-1}): 16.74 ± 4.47 T_{max} (min): 15.00 ± 0.00 $T_{1/2,\lambda z}$ (min): 770.36 ± 65.01 $V_d/F_{\lambda z}$ (L/kg): 60,036.51 ± 19,704.59 CL/F (L/h/kg): 4,999.34 ± 1,198.79	
Male Beagle Dog	1 (i.v.)	100 mg/kg	1	AUC (mg/h/L): 1979.31 ± 1140.31, Ka (h): 10.2843 ± 2.5,	(Sheng et al. 1993)

(*continued*)

Table 8. Continued.

Subjects/animals	Drug administered	Dosages	Detected compounds	Pharmacokinetic parameters	References
				$t_{1/2\alpha}$ (h): 0.15 ± 0.26, $t_{1/2\beta}$ (h): 12.59 ± 8.83, CL (h): 60.70 ± 24.38, Vd (L): 699.53 ± 219.05	
	1 (i.g.)	280 mg/kg	1	AUC (μg·h/L): 777.29 ± 150.10, C_{max} (μg/L): 15.46 ± 4.20, T_{max} (h): 3.71 ± 0.95, $t_{1/2\alpha}$ (h): 0.63 ± 0.14, $t_{1/2\beta}$ (h): 34.82 ± 14.36, CL (h): 2.64 ± 0.55, Vd (L): 125.41 ± 32.55	
Male Wistar rats	CRE (i.g.)	1.2 g/kg	1	AUC (h·ng/mL): 707.91, $T_{1/2}$ (h): 1.89, C_{max} (ng/mL): 315.78, T_{max} (h): 1	(Bao et al. 2010)
			4	AUC (h·ng/mL): 130.29, $T_{1/2}$ (h): 1.71, T_{max} (h): 1	
		2.4 g/kg	1	AUC (h·ng/mL): 1220.32, $T_{1/2}$ (h): 2.29, C_{max} (ng/mL): 501.58, T_{max} (h): 1	
			4	AUC (h·ng/mL): 348.61, $T_{1/2}$ (h): 2.64, T_{max} (h): 1	
		4.8 g/kg	1	AUC (h·ng/mL): 2424.62, $T_{1/2}$ (h): 4.79, C_{max} (ng/mL): 584.57, T_{max} (h): 1	
			4	AUC (h·ng/mL): 872.76, $T_{1/2}$ (h): 5.89, T_{max} (h): 1	
Male Wistar rats	CRE (i.v.)	10.2 mg/kg	1	Hippocampus: AUC (ng·h/g): 6940 ± 206, C_{max} (ng/g): 272 ± 12, $T_{1/2K\alpha}$ (h): 4.48 ± 1.7 $T_{1/2\alpha}$ (h): 0.215 ± 0.063 $T_{1/2\beta}$ (h): 12.0 ± 1.5, T_{max} (h): 3.67 ± 0.48 Plasma: AUC (ng·h/mL): 473 ± 18, $T_{1/2\alpha}$ (h): 0.227 ± 0.017, $T_{1/2\beta}$ (h): 1.13 ± 0.18 Vd (mL/kg): 2400 ± 300 CL (mL·kg/h): 6400 ± 200	(Wang et al. 2005)
Male healthy volunteers	300 mg 1 (p.o.)	300 mg/kg	1	AUC (mg·h/L): 2799 ± 1128.5, C_{max} (mg/L): 394.7 ± 155.4, T_{max} (h): 2.37 ± 0.04, $T_{1/2K\alpha}$(h): 0.87 ± 0.03, $T_{1/2\beta}$ (h): 2.94 ± 0.14	(Li & Zhang 1997)
Male Wistar rats	CRE (i.g.)	300 mg/kg	1	AUC_{0-t} (ng·h/mL): 92.71 ± 15.03, C_{max} (ng/mL): 12.27 ± 3.30, T_{max} (h): 1.90 ± 0.58, $T_{1/2}$ (h): 3.96 ± 0.92	(Liu et al. 2014)
			4	AUC_{0-t} (ng·h/mL): 4.72 ± 0.79, C_{max} (ng/mL): 0.74 ± 0.44, T_{max} (h): 1.30 ± 0.40, $T_{1/2}$ (h): 3.91 ± 0.80	
			3	AUC_{0-t} (ng·h/mL): 1.39 ± 0.60, C_{max} (ng/mL): 1.38 ± 0.54, T_{max} (h): 14.28 ± 2.38, $T_{1/2}$ (h): 4.02 ± 1.83	
			5	AUC_{0-t} (ng·h/mL): 6.63 ± 1.70, C_{max} (ng/mL): 1.05 ± 0.75, T_{max} (h): 1.38 ± 0.54, $T_{1/2}$ (h): 5.28 ± 1.44	
			8	AUC_{0-t} (ng·h/mL): 7.11 ± 0.65, C_{max} (ng/mL): 0.67 ± 0.23, T_{max} (h) 1.38 ± 0.54, $T_{1/2}$ (h): 4.35 ± 0.67	

Notes: AUC: area under curve; C_{max}: maximum concentration; CL: body clearance; i.g.: intragastric; i.v.: intravenous; MTT: mean transit time; p.o.: per os; $T_{1/2}$: half-life; $T_{1/2a}$: distribution half-life; $T_{1/2\beta}$: elimination half-life; $T_{1/2K\alpha}$: absorption half-life; T_{max}: time to peak concentration; Vd: volume of distribution.

acute toxicity study showed that the oral medial lethal dose (LD_{50}) of the fibrous roots of CR was greater than 7000 mg/kg body weight in Kunming mice. A sub-chronic toxicity study showed that the no-observed-adverse effect level (NOAEL) was 1.88 g/kg body weight in rats, whereas 3.76 g/kg body weight resulted in liver and lung damage. An Ames test, a mouse micronucleus test, and a mouse sperm abnormality test provided negative results (Ning et al. 2015). The median acute oral lethal dose of the CRE was 2.95 g/kg in mice; however, the alkaloid-rich extract was much more toxic than the total extract of CR (Ma et al. 2010). In another study, the LD_{50} values of four alkaloids (berberine, coptisine, palmatine and epiberberine) were determined as 713.57, 852.12, 1533.68 and 1360 mg/kg, respectively. Likewise, the cytotoxicity of berberine was the highest and that of palmatine was the lowest toward HepG2 and 3T3-L1 cells. In a subchronic toxicity study, no mortality or morbidity was observed (Yi et al. 2013). To determine the NOAEL and the toxicity of CR, rats received repeated oral administration of CR for 13 weeks. No mortality or remarkable clinical signs were observed during this 13-week study. The NOAEL of CR was determined as 667 mg/kg/day for male rats and 2000 mg/kg/day for female rats (Lee et al. 2014). Oral berberine has caused respiratory failure, extrapyramidal system reactions, severe arrhythmia, liver function injury and even death in clinics in China (Li et al. 2008), which as believed to caused by its inhibitory effect on the human eag-related gene (hERG) potassium channel and induction of mitochondrial dysfunction (Pereira et al. 2008; Schramm et al. 2011). Furthermore, the authors reported that an AChE inhibitor significantly increased the acute toxicity of the CRE, whereas a cholinesterase reactivator significantly decreased the acute toxicity. Therefore, the authors suggested that the acute toxicity of the oral CR extract was related to AChE inhibition (Ma et al. 2011) Taking these findings together, we concluded that the toxic constituents of CR were the alkaloids, mainly berberine. However, the toxic mechanism of the CR alkaloids may be complicated and remains to be determined. The currently recommended doses of CR alkaloids and CR consumption are relatively safe (Ho et al. 2014). In fact, CR is seldom used alone in clinics; instead, it is usually prescribed with other medicines that could reduce its toxic effect.

Future perspectives and conclusions

Herbal medicines, including TCMs, are considered useful agents to treat various human diseases (Li et al. 2009; Peng et al. 2018). CR has a long history of being used as an important herbal medicine in Asian countries because of its reliable curative effects against various diseases. Nowadays, the most predominant traditional uses of CR have been confirmed by modern pharmacological research. So far, these investigations have reported that CR contains abundant isoquinoline alkaloids (especially berberine), which are also the active substances responsible for the pharmacological effects of this TCM. CR and berberine have a broad-spectrum antibacterial effect, manifesting as bacteriostasis at low concentrations and sterilization at high concentrations. This suggests that a combination of berberine or CR and conventional antibacterial drugs might exert a greater effect. Intensive research has indicated that CR has potential as a cardioprotective agent. In addition to reducing the incidence, it also protects the heart from MI/R injury. These properties are mainly attributed to berberine, coptisine, palmatine, epiberberine, jatrorrhizine and magnoflorine. Many studies have demonstrated modulation of the composition of the gut microbiota (enrichment of beneficial microbiota and inhibition of harmful microbiota) as one of the most important aspect for treating obesity, diabetes, and other metabolic disorders. As a natural compound with both anti-inflammatory and antitumor activities, berberine shows great potential in cancer treatment. However, the effects of berberine are not strong; therefore, structural modification of berberine is required. Moreover, CR containing various active components may be more effective than its single component berberine and could provide multiple therapeutic effects. There is a significant difference between the blood concentration and the tissue concentration. Therefore, to find a suitable pharmacokinetic marker for CR may be challenging but is necessary. Moreover, the pharmacokinetics of TCM should try to elucidate all the chemical components entering the body and their processes in the body (absorption, distribution, metabolism and excretion), with the aim of building a bridge between the complex chemical components and the systemic clinical effects, to reveal the underlying mechanism(s). Additionally, related target-organ toxicity evaluations are lacking. Thus, more work should be devoted to investigating the pharmacokinetics and features of CR and its active components, and further clinical studies are required to evaluate the potential curative effects and possible toxicities of CR and its active components toward the target organs. In addition, according to the current pharmacological research, berberine is not only the main active component but also the primary toxic component of CR. Consequently, it is crucial to develop a strategy to balance the pharmacological effects and toxicity of berberine. Besides, current reports on the original plants used to make CR, including *C. chinensis*, *C. deltoidea* and *C. teeta*, commonly focus on the chemical components and pharmacological effects of the roots because of their traditional use in TCM, and the other parts of the plants are often ignored and disposed of without pretreatment (Shen 2006). However, some previous reports revealed that the leaves of the CR plants also contain berberine (Li et al. 2004; Liu T et al. 2010). Therefore, further research is required to investigate the chemical constituents and pharmacological activities of the other parts of the original CR plants.

This present study systematically reviewed the traditional uses, botany, phytochemistry, pharmacology, and toxicology of CR to provide comprehensive information regarding this herbal medicine, which could be beneficial for highlighting the importance of CR and providing some clues for the future research of this herbal medicine.

Consent for publication

All authors have provided consent for publication in Pharmaceutical Biology.

Disclosure statement

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