

A comprehensive review of traditional uses, phytochemistry and pharmacology of *Reynoutria* genus

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Abstract

Objectives The genus *Reynoutria* belonging to the family Polygonaceae is widely distributed in the north temperate zone and used in folk medicine. It is administered as a sedative, tonic and digestive, also as a treatment for canities and alopecia. Herein, we reported a review on traditional uses, phytochemistry and pharmacology reported from 1985 up to early 2022. All the information and studies concerning *Reynoutria* plants were summarized from the library and digital databases (e.g. ScienceDirect, SciFinder, Medline PubMed, Google Scholar, and CNKI).

Key findings A total of 185 articles on the genus *Reynoutria* have been collected. The phytochemical investigations of *Reynoutria* species revealed the presence of more than 277 chemical components, including stilbenoids, quinones, flavonoids, phenylpropanoids, phospholipids, lactones, phenolics and phenolic acids. Moreover, the compounds isolated from the genus *Reynoutria* possess a wide spectrum of pharmacology such as anti-atherosclerosis, anti-inflammatory, antioxidative, anticancer, neuroprotective, anti-virus and heart protection.

Summary In this paper, the traditional uses, phytochemistry and pharmacology of genus *Reynoutria* were reviewed. As a source of traditional folk medicine, the *Reynoutria* genus have high medicinal value and they are widely used in medicine. Therefore, we hope our review can help genus *Reynoutria* get better development and utilization.

Keywords: *Reynoutria*; traditional uses; phytochemistry; pharmacology

Introduction

The genus *Reynoutria*, a genus of the family Polygonaceae, is mainly distributed in the wide temperate areas of the northern hemisphere. This genus comprises about seven species, five of which were discovered in China. As a country that has been using herbal medicine to treat diseases since ancient times, China has abundant natural drug resources and experience in clinical application. The plants of the genus *Reynoutria*, with rich chemical compositions and pharmacological activities, have been used in Traditional Chinese medicines or folk medicines to treat various diseases, which have become a hot spot for phytochemical studies.^[1] Currently, more than 277 compounds have been extracted and identified from the genus *Reynoutria*, with stilbenoids,^[2] quinones^[3] and flavonoids^[4] being major compounds. Meanwhile, several studies showed that the compounds and extracts isolated from the genus *Reynoutria* possessed a wide spectrum of pharmacology *in vivo* or *in vitro* such as anti-atherosclerosis,^[5] anti-inflammatory,^[6] antioxidative,^[7] anticancer,^[8] neuroprotective,^[9] anti-virus,^[10] heart protection,^[11] hair darkening.^[12] So, it is necessary for better research to review the genus *Reynoutria*. In this study, we comprehensively summarized research on the traditional uses, phytochemistry, and pharmacology of the genus *Reynoutria*. The extant information on these species

allows us to provide a scientific basis for future research studies and to explore their potential therapeutic use.

Search strategy

Comprehensive research and analysis of previously published literature were conducted for studies on the traditional use, distribution, chemistry and pharmacological properties of the genus *Reynoutria*. The search was conducted using databases such as ScienceDirect, SciFinder, Medline PubMed, Google Scholar, Baidu Scholar and CNKI by using the keywords such as *Reynoutria*, *Reynoutria japonica*, *Reynoutria ciliinervis* and *Reynoutria multiflora*. Meanwhile, since some of the main *Reynoutria* species have long been reported as *Fallopia* species, we also used other keywords such as ‘*Fallopia japonica*’ and ‘*Fallopia multiflora*’ in the search strategy. Furthermore, part of the analyzed studies was got by a manual search of articles in the reference lists of the included studies. The PRISMA template for determining the list of the article is displayed in [Figure 1](#). The chemical structures were drawn using ChemDraw Professional 20.0 software.

Traditional uses

Genus *Reynoutria* has seven species all over the world, which included *Reynoutria × bohemica* Chrtek & Chrtková,

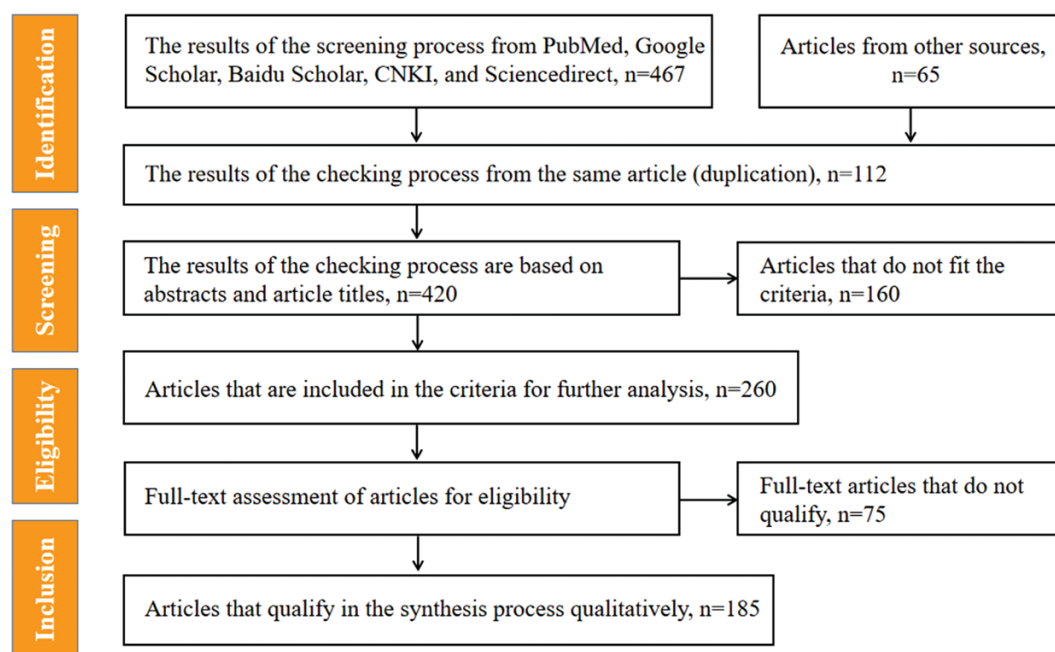


Figure 1 Research data search and selection flow.

Reynoutria ciliinervis (Nakai) Moldenke, *Reynoutria compacta* (Hook.f.) Nakai, *Reynoutria forbesii* (Hance) T.Yamaz., *Reynoutria japonica* Houtt., *Reynoutria multiflora* (Thunb.) Moldenke, *Reynoutria sachalinensis* (F.Schmidt) Nakai.^[13] *Reynoutria* plants originated in Asia, and six species of the genus are known. Due to human activities, *Reynoutria* plants were introduced into Europe and North America, and resulted in the hybrid species *Reynoutria* × *bohemica*.^[14] Among them, the tuberous root of *R. japonica* and *R. multiflora* known as “Hu Zhang” and “He Shouwu”, respectively, are famous Traditional Chinese medicines in China.^[15, 16] Meanwhile, *R. compacta*, *R. ciliinervis* and *R. forbesii* also have been reported as folk herbs.^[17–20] A summary of their local names, geographical distribution and traditional uses were presented in Table 1. The distribution of genus *Reynoutria* in the world is shown in Figure 2.

Phytochemistry

Currently, approximately 277 chemical components have been isolated and identified from the genus *Reynoutria*. The fundamental chemical constitutions are stilbenoids, quinones, and chromones. In this article, 277 compounds have been reported, including 58 stilbenoids (1–58), 51 quinones (59–109), 48 flavonoids (110–157), 21 phenylpropanoids (158–178), 9 phospholipids (179–187), 9 lactones (188–196), 23 phenolics and phenolic acids (197–219), 19 fatty acids (220–238), and 39 other compounds (239–277), which are shown in Figures 3–15 and Table 2.

Stilbenoids

The stilbenoids are divided into two groups, one with 2,3,5,4'-tetrahydroxy stilbene (1–19) and the other with resveratrol (20–40). 2,3,5,4'-Tetrahydroxy stilbene glycosides mostly form glycosides at the 2-hydroxy position and the glucose group's 2-position hydroxy often be replaced by different groups (Figure 3). While resveratrol glycosides mostly form glycosides at the 3-hydroxy or 4'-hydroxy position (Figure 4).

It is worth noting that most stilbenoids are *trans*-stilbenoids, which may be related to the stronger photostability of *trans*-stilbenoids. Furthermore, 17 stilbenoid glycoside dimers (42–58) have been isolated from *R. multiflora* (Figure 5), which often consist of two stilbenes units polymerized.

Quinones

Quinones can be divided into anthraquinones (59–85), naphthoquinones (86–93), benzoquinones (94–95) and dianthrones (96–109). Among them, anthraquinones are emodin-type anthraquinones, whose 1,8-hydroxy positions are easy to form ethers and glycosides with methyl and sugar groups. All reported naphthoquinones are α -(1,4) naphthoquinones (Figure 6). Meanwhile, the dianthrones (Figure 7) mostly exist in the form of intermediate linkage and form glycosides at the 8 position.

Flavonoids

According to structures, 48 flavonoids are divided into chromones (110–122), flavones (123–139), flavanones (140–155), isoflavone (156) and flavonone (157).

Chromones are a group of natural compounds that are commonly found in plants. The oxygen-containing heterocycles are the core of flavonoid. Mostly chromones (Figure 8) are substituted at the 2, 5, and 7 positions and form glycosides at the 7 position. Flavonoid's basic parent nucleus is 2-phenyl chromone. Notably, flavones (Figure 9) mostly form glycosides with various sugars at the 3 position. Whereas flavanones (Figure 10) rarely form glycosides, they're more often replaced by galloyl at the 3 position. Meanwhile, flavanones can form dimer or trimer.

Phenylpropanoids

Phenylpropanoids, a class of compounds consisting of a benzene ring linked to three carbons (C6–C3), can be divided into simple phenylpropanoids (158–166), coumarins (167–171) and lignans (172–178) (Figure 11). This type of component is

Table 1 Traditional uses of the genus *Reynoutria*

Species	Local name	Parts	Distribution	Dosage forms	Traditional uses
<i>R. multiflora</i> (Thumb.) Moldenke	Heshouwu Chishouwu	Tuberous roots	China (Shaanxi, Gansu, Sichuan, Yunnan, and Guizhou), Japan, Korea, Thailand, Vietnam, Europe and North America.	Decoction, vinum, pill, powder (taken orally); ointment, powder, liniment (external application); Decoction (taken orally); liniment (external application)	Anti-aging, lowering blood lipids, anti-atherosclerosis, enhancing immunity, intelligence-enhancing, anti-bacteria and anti-myocardial ischemia[1]
<i>R. ciliinervis</i> (Nakai) Moldenke	Yejiatong Shouwuteng	Stems			Sedative, hypnotic, hyperglycemia, lipid-lowering and anti-inflammatory[17]
	Zhushaqi (Shaanxi), Hongyaazi (Henan)	Tuberous roots	China (Jilin, Liaoning, Henan, Shaanxi, Gansu, Qinghai, Hubei, Sichuan, Guizhou and Yunnan), Korea.	Decoction, vinum, powder (taken orally); powder, ointment, liniment (external application)	Acute stomach pain, enterogastritis, amygdalitis, shigellosis, lumbago, tract infection and traumatic injury[19]
<i>R. japonica</i> Houtt.	Huzhang Zilonggen (Anhui)	Tuberous roots	China (Liaoning, Jilin, Henan, Shaanxi, Gansu and Sichuan), Europe and North America.	Decoction (taken orally); ointment, liniment (external application)	Anti-inflammation, pain relief, high blood pressure, high cholesterol, anti-tumor, hemostasis and enhancing immunity[18]
<i>R. compacta</i> (Hook.f.) Nakai	Huoxuelong Suantongzi	Tuberous roots	China (Sichuan and Yunnan), Japan, Korea and Europe.	Decoction (taken orally)	Rheumatism, relieving cough and expelling phlegm[19]
<i>R. forbesii</i> (Hance) T.Yamaz.	Manshouwu Manhuzhang	Tuberous roots	China (Henan, Shaanxi, Hubei, Sichuan, Guizhou and Yunnan), Japan[20]	-	-

“-” means no reports were found

less distributed in the genus *Reynoutria*. Notably, vanicosides A (164) and B (165) were reported from *R. sachalinensis*, which could induce an apoptotic death pathway in the melanoma cell lines.

Phospholipids

Phospholipids are an important class of lipid concomitants, which are present in almost all cells of plants and animals. A total of 9 phospholipids (179–187) (Figure 12) are obtained from the genus *Reynoutria*.

Lactones

Lactones are formed by the esterification of molecules containing both carboxyl and hydroxyl groups. The characteristic of lactone is that there is only one ester group in the ring. Now 9 lactones (188–196) are reported from the genus *Reynoutria*. The structures of the specific compounds are shown in Figure 12.

Phenolics and phenolic acids

Phenolic compounds are important secondary metabolites in plants, which have good antioxidant activity for the existence of phenolic hydroxyl and phenolic compounds. While phenolic acid is a kind of organic acid containing a phenol ring. A total of 20 phenolics (197–216) and 3 phenolic acids (217–219) have been isolated from the genus *Reynoutria*. The structures of specific compounds are shown in Figure 13.

Fatty acids

Fatty acids are the main components of neutral fat, phospholipids and glycolipids. According to the chain length, fatty acids can be divided into short-chain fatty acids, medium-chain fatty acids, and long-chain fatty acids. A total of 19 fatty acids (220–238), mostly long chain saturated fatty acids, were reported in the genus *Reynoutria* (Figure 14).

Other compounds

In addition, 39 other compounds are isolated from the genus *Reynoutria*, including 3 saccharides (239–241), 4 polyols (242–245), 5 steroids (246–250), 6 terpenoids (251–256), 6 alkaloids (257–262) and 15 miscellaneous compounds (263–277). Specific compounds structure are shown in Figure 15.

Pharmacology activities

Anti-atherosclerosis

The compound 2,3,5,4'-tetrahydroxystilbene-2-O-β-D-glucoside (TSG) from the genus *Reynoutria* has a protective effect on vascular endothelium. *In vitro*, 50 or 100 μM TSG could block the (transforming growth factor-β/drosophila mothers against decapentaplegic protein) TGFβ/Smad signal pathway and improve the endothelial dysfunction of umbilical veins caused by tumor necrosis factor α (TNF-α).[88] TSG (1 or 10 μmol/l) protected umbilical vein endothelium from LPS damage by inhibiting mitochondria-dependent apoptotic pathway,[90] which also could ameliorate lysophosphatidylcholine (LPC)-induced umbilical vein endothelial cell injury through ROS/p-JNK pathway,[91] and inhibit LPC-induced vascular endothelial growth factor (VEGF) and VEGF165mRNA expression.[92] TSG (1 × 10⁻⁵ mol/l) inhibited vascular smooth muscle cell proliferation via the NO/cyclic guanosine monophosphate/cGMP-dependent protein

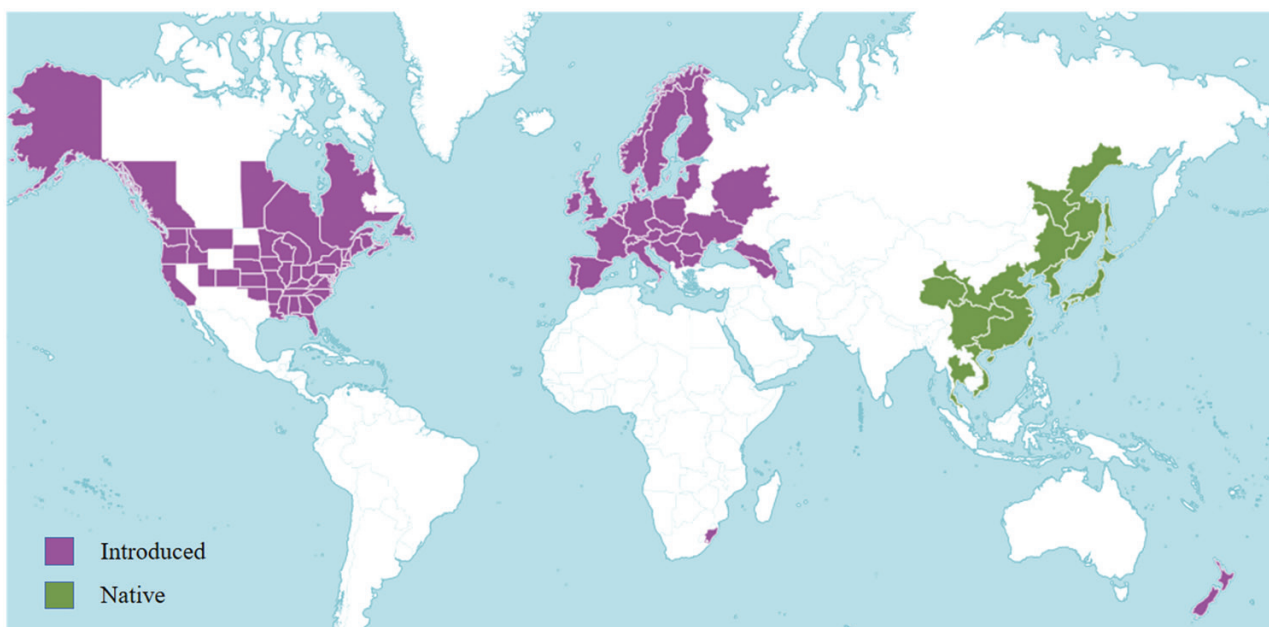


Figure 2 Distribution of genus *Reynoutria* in different regions of the world.

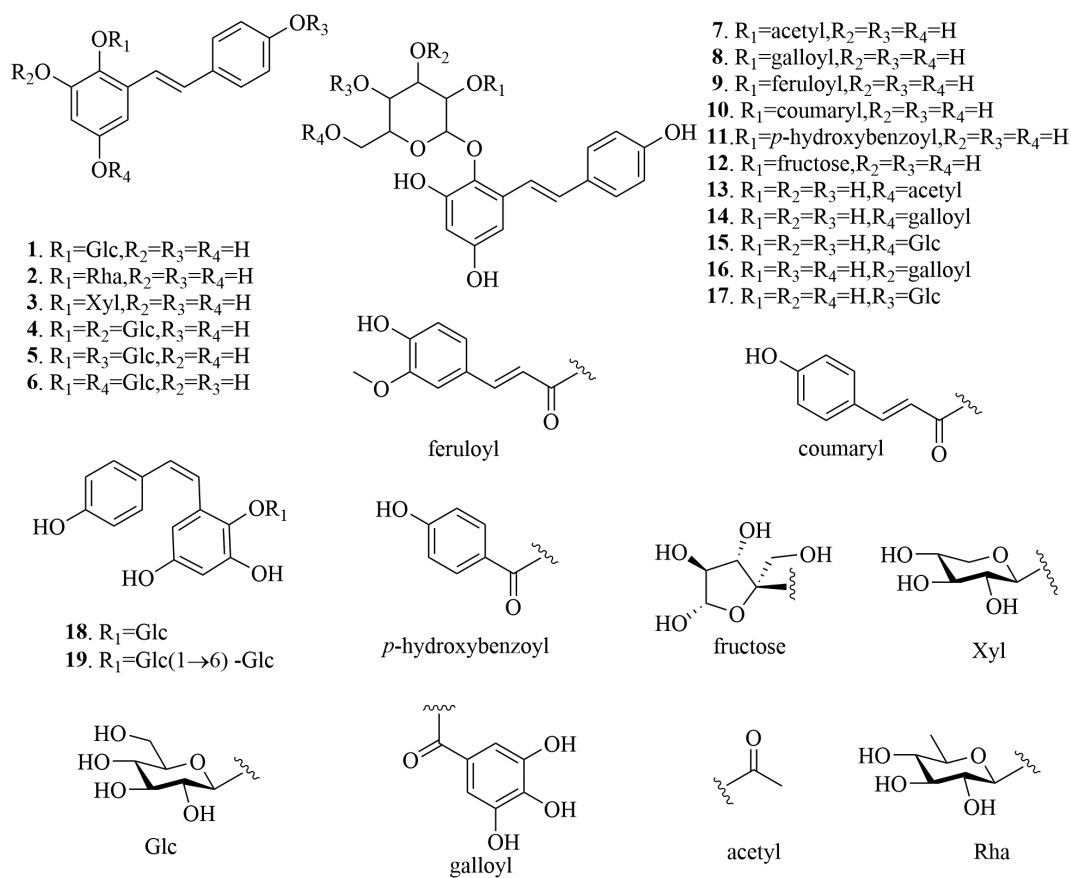


Figure 3 Structure of 2,3,5,4'-tetrahydroxystilbene glucoside in the genus *Reynoutria*.

kinase (NO/cGMP/PKG) pathway.^[93] In vivo, TSG (100 mg/kg/day) inhibited excessive autophagy in vascular tissue and improved microvascular endothelial dysfunction by activating the protein kinase B/mammalian target of the rapamycin (Akt/mTOR) pathway.^[94] In addition, studies showed

that TSG (60 or 120 mg/kg/day) could restore endothelial diastole and remodel the aortic intima.^[95] Meanwhile, emodin (20 or 40 mg/kg) could treat atherosclerosis through Janus kinase 2/Signal Transducer and Activator of Transcription 3 (JAK2/STAT3) cell signal pathways.^[96] Hyperlipidemia is also

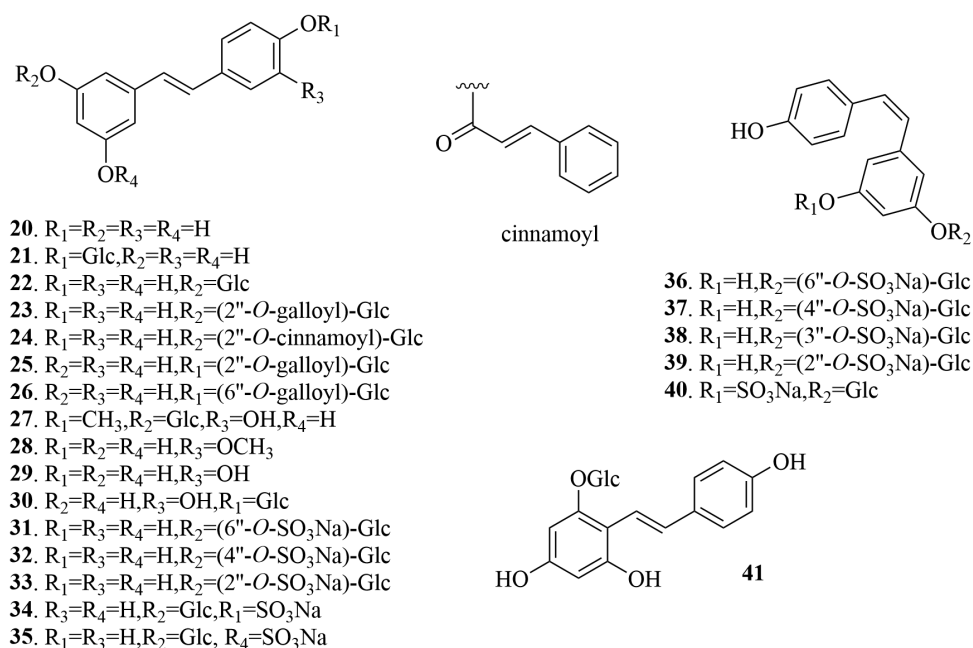


Figure 4 Structure of resveratrol glucoside in the genus *Reynoutria*.

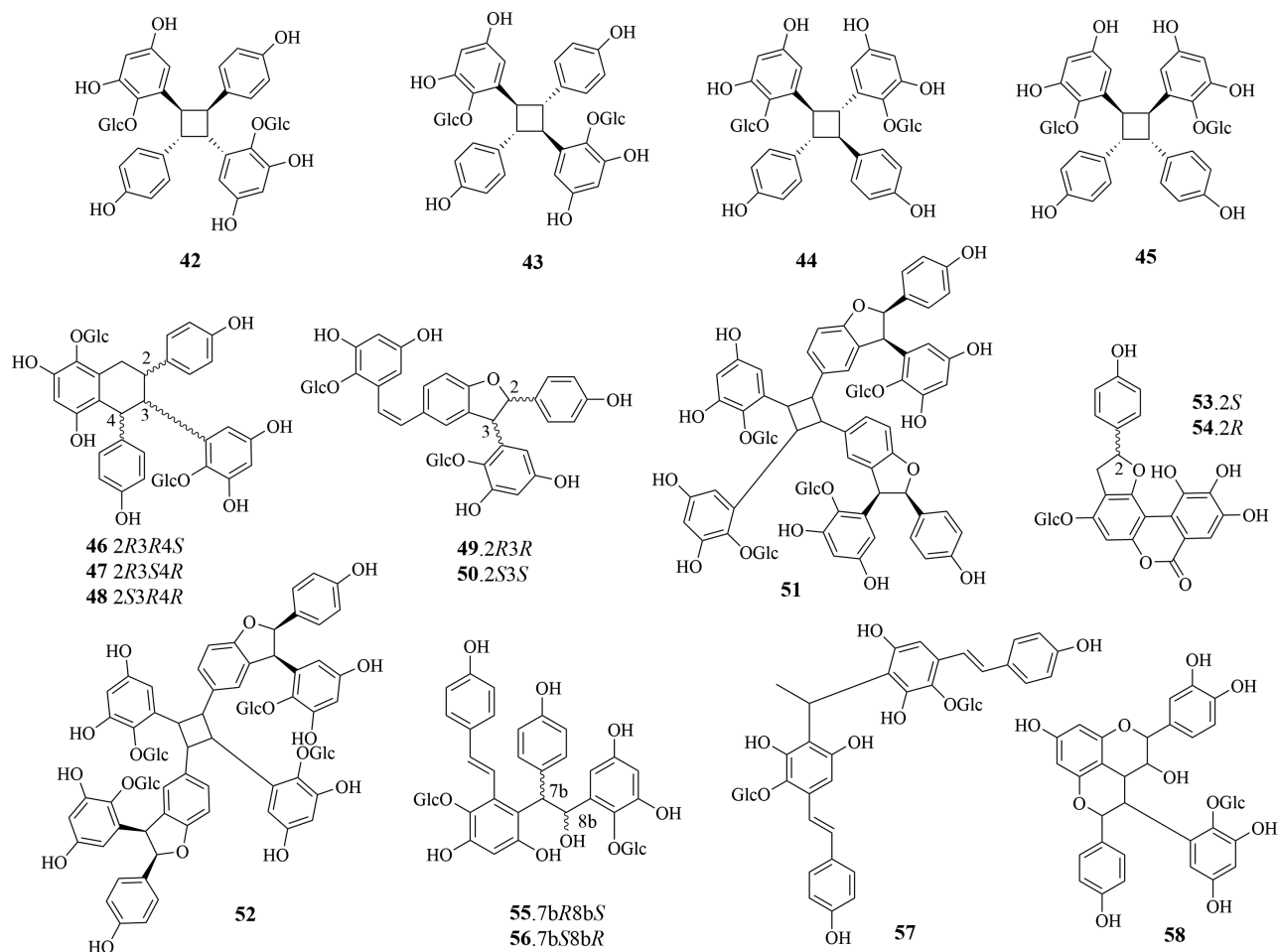


Figure 5 Structure of stilbene glycoside dimers in the genus *Reynoutria*.

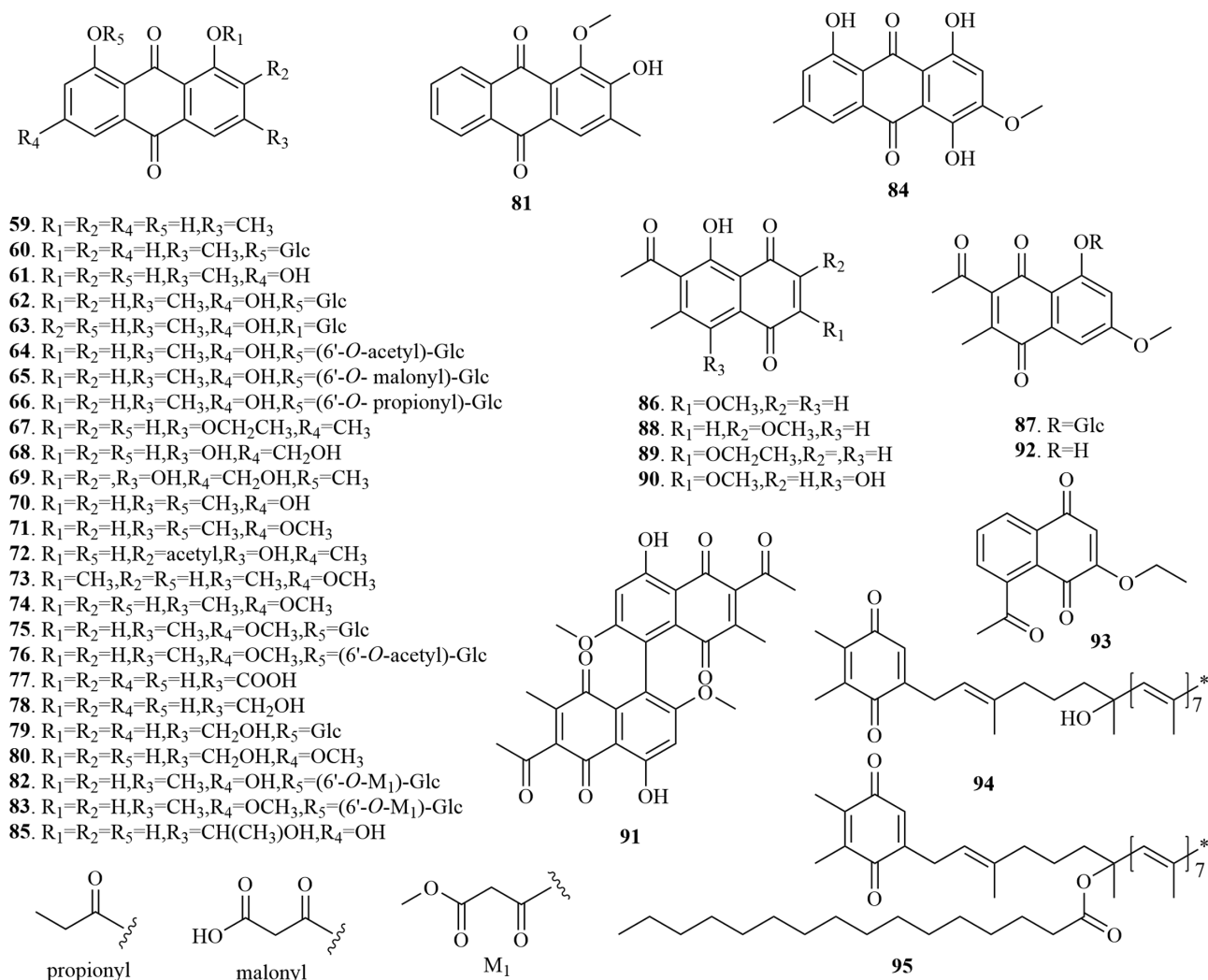


Figure 6 Structure of anthraquinones, naphthoquinones, and benzoquinones in the genus *Reynoutria*.

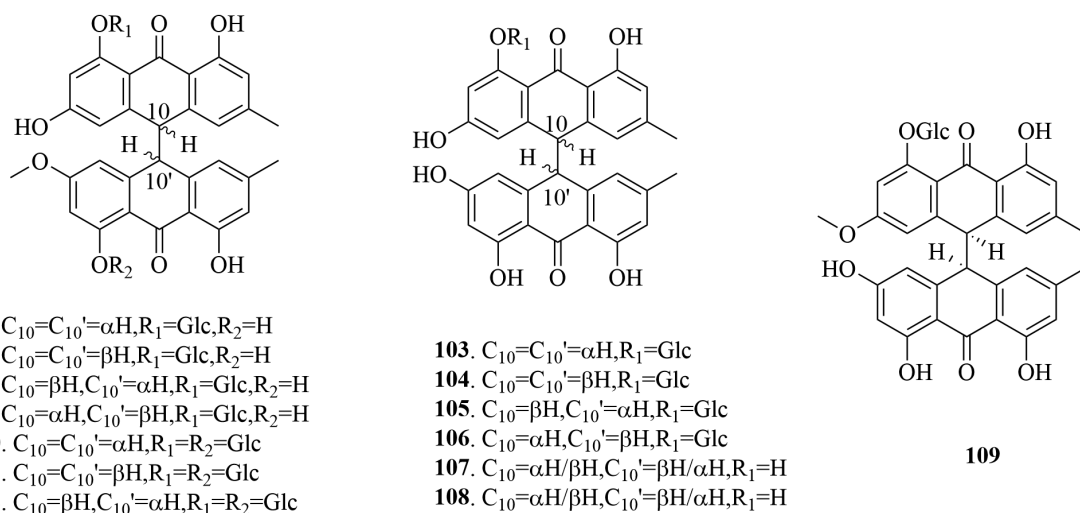


Figure 7 Structure of dianthrone in the genus *Reynoutria*.

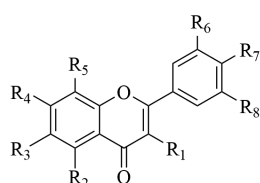
thought to be a cause of atherosclerosis. *R. multiflora* 70% ethanol extract (16.2 g/kg) was able to significantly reduce blood lipids.^[97] Polydatin (50 or 100 mg/kg/day) could reduce

total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) in hyperlipidemic rabbits^[98] and high-fat/high-cholesterol-fed hamsters.^[99]



110. $R_1=CH_3, R_2=R_3=OH$
 111. $R_1=R_2=CH_3, R_3=OH$
 112. $R_1=CH_2CHOHCH_3, R_2=CH_3, R_3=OGlc$
 113. $R_1=CH_2CHOHCH_3, R_2=CH_3, R_3=O$ -fucopyranosyl (1→2) -Glc
 114. $R_1=CH_3, R_2=CH_2COOH, R_3=OH$
 115. $R_1=CH_3, R_2=CH_2COOCH_3, R_3=OH$
 116. $R_1=CH_3, R_2=CH_2OH, R_3=OH$
 117. $R_1=CH_3, R_2=COOH, R_3=OH$
 118. $R_1=CH_2CHOHCH_3, R_2=CH_2COOH, R_3=OH$
 119. $R_1=R_2=CH_3, R_3=OGlc$
 120. $R_1=CH_3, R_2=OH, R_3=OGlc$
 121. $R_2=CH_3, R_3=OH, R_1=CH=C(CH_3)OGlc$

Figure 8 Structure of chromones in the genus *Reynoutria*.



123. $R_1=R_3=R_5=H, R_2=R_4=R_7=OH, R_6=R_8=OCH_3$
 124. $R_1=R_3=R_5=R_6=R_8=H, R_2=R_4=R_7=OH$
 125. $R_1=R_3=R_5=H, R_2=R_7=OH, R_6=R_8=OCH_3, R_4=OGlc$
 126. $R_1=R_3=R_6=R_8=H, R_2=R_4=R_7=OH, R_5=OGlc$
 127. $R_1=R_5=R_6=H, R_2=R_4=R_7=R_8=OH, R_3=OGlc$
 128. $R_1=R_2=R_4=R_7=OH, R_3=R_5=R_6=R_8=H$
 129. $R_1=R_2=R_4=R_6=R_7=OH, R_3=R_5=R_8=H$
 130. $R_2=R_4=R_6=R_7=OH, R_3=R_5=R_8=H, R_1=OGlc$
 131. $R_2=R_4=R_6=R_7=OH, R_3=R_5=R_8=H, R_1=OGal$
 132. $R_2=R_4=R_7=R_8=OH, R_3=R_5=R_6=H, R_1=OGlc(1\rightarrow6)$ -Rha
 133. $R_2=R_4=R_6=R_7=OH, R_3=R_5=R_8=H, R_1=OAra$
 134. $R_2=R_4=R_6=R_7=OH, R_3=R_5=R_8=H, R_1=ORha$
 135. $R_2=R_4=R_6=R_7=OH, R_3=R_5=R_8=H, R_1=OXyl$
 136. $R_1=R_2=R_4=R_7=OH, R_3=R_6=R_8=H, R_5=CH_2CH_2C(CH_3)_2OH$
 137. $R_2=R_7=OH, R_3=R_5=R_6=R_8=H, R_1=R_4=ORha$
 138. $R_2=R_4=R_6=R_7=OH, R_3=R_5=H, R_1=OCH_3, R_8=OXyl$
 139. $R_1=R_3=R_5=R_6=H, R_2=R_7=R_8=OH, R_4=OGlc$

Figure 9 Structure of flavones in the genus *Reynoutria*.

Anti-inflammatory

In vitro, it was reported that TSG (50 μ M) could achieve anti-inflammatory effects by reducing LPS-induced pro-inflammatory cytokine release.^[100] Crude extract of *R. japonica* and emodin (40 mg/kg) both inhibited chemotaxis through inhibition of the Mitogen-activated protein kinase/extracellular regulated protein kinases (MEK/ERK) pathway, resulting in anti-inflammatory effects.^[101] In addition, emodin (20 μ g/mL) can reduce the activation of NF- κ B in RAW264.7 cells and achieve a good anti-inflammatory effect.^[102] *In vivo*, 10 μ M polydatin could inhibit the NLRP3 inflammasome pathway and reactive oxygen species (ROS) production.^[103] Meanwhile, TSG (60 mg/kg) significantly up-regulated peroxisome proliferators-activated receptors (PPAR)- γ and inhibited the NF- κ B pathway, which could ameliorate acetic acid-induced colitis injury.^[104] Chlorogenic acid (120 mg/kg/day) could alleviate DSS-induced mucosal injury and

reduce the expression of a series of inflammatory-related proteins, which was related to the MAPK/ERK/JNK signaling pathway.^[105]

Anti-oxidative

TSG had good free radical scavenging ability and could attenuate the (1-methyl-4-phenylpyridinium) MPP⁺-induced rise in ROS levels in PC12 cells to achieve antioxidant effects.^[106] It produced antioxidant effects by modulating superoxide dismutase (SOD)-3 and GST-4, which could improve the survival time of *Caenorhabditis elegans*.^[7] Moreover, 50 μ M TSG could increase SOD and Glutathione peroxidase (GSH-Px) activities in serum and organs of galactose-aging rats; reduced 2-thiobarbituric acid content to achieve antioxidant effects.^[7] Both polydatin and resveratrol (200 mg/kg) showed significant antioxidant activity.^[107] *R. multiflora* acidic polysaccharides had good 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity and anti-proliferative activity.^[108] Likewise, *R. multiflora* polysaccharides also had high hydroxyl radical scavenging activity.^[109]

Anti-cancer

It was shown that 50 μ M emodin significantly inhibited the proliferation of RAW 264.7 cells through the Ca²⁺-STAT pathway.^[110] Meanwhile, emodin and emodin-8-methyl ether inhibited the growth of human colon cancer cells by inhibiting Recombinant Cell Division Cycle Protein 25B (Cdc25B) phosphatase (IC₅₀ = 62.5, 30, 34 μ g/ml, respectively).^[111] Whereas emodin-8-O-glucoside and physcion-8-O-glucoside possessed farnesyl protein transferase (FPTase)^[60] (IC₅₀ = 46.3 and 28.2 μ g/ml, respectively). What is noteworthy is that rhein could reverse the drug resistance in doxorubicin-resistant SMMC-7721 cells, IC₅₀ = 26.81 μ M,^[112] polydatin (6 μ M) inhibited AMC-HN-8 and HeLa cells proliferation and induced apoptosis by inhibiting platelet-derived growth factor (PDGF)/AKT signal pathway,^[113] and 80 or 120 μ M chrysophanol suppressed the proliferation of SNU-C5 cells by inhibiting the overexpression of epidermal growth factor receptor (EGFR).^[114] The extract of *R. multiflora* roots (100 or 200 μ g/ml) was able to inhibit MCF-7 cells and promote apoptosis.^[115]

Neuroprotective

It has been shown that TSG (6.25–50 μ M) could inhibit MPP⁺ cytotoxicity in SH-SY5Y cells by protecting mitochondrial function, and preventing caspase-3 activation.^[116] And TSG (200 μ M) could protect rat hippocampus neuron cells through phosphatidylinositol 3 kinase (PI3K)/Akt signal pathway and mitochondrial apoptotic pathways,^[117] which also could prevent 6-OHDA-induced apoptosis in PC12 cells by regulating the ROS-NO signal pathway (10–50 μ M)^[118] and protect HT22 cells by suppressing glutamate-induced disruption of MMP and anion channel-1 (30–200 μ g/ml).^[119] The hexane extract of *R. multiflora* (0.1–10 μ g/ml) may inhibit glutamate-induced apoptosis cortical neurons by inhibiting death receptor 4 (DR4) and caspase activation.^[120] The water extract of *R. multiflora* (0.1–10 μ g/ml) exerted a protective effect on hippocampal neurons by inhibiting brain-derived neurotrophic factor (BDNF) expression and cyclic adenosine monophosphate (cAMP)-response element binding protein (CREB) phosphorylation.^[121] Notably, emodin (10–40 μ M) could induce Neuro2a cell regeneration by activating

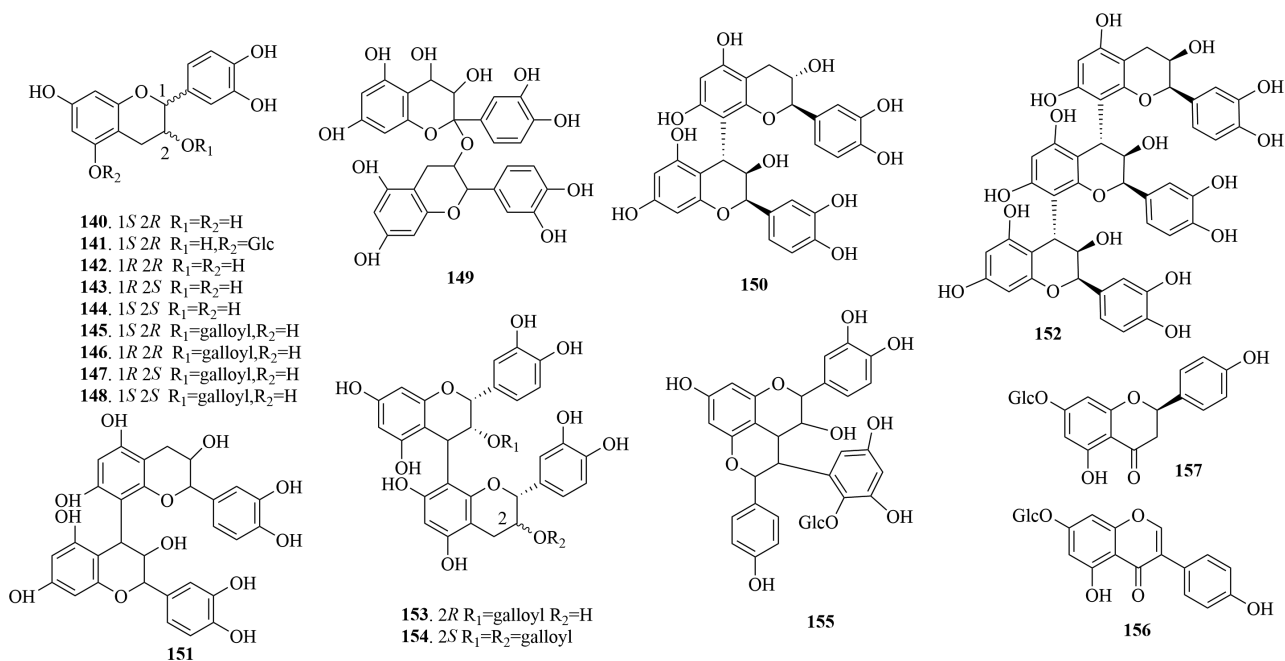


Figure 10 Structure of flavanones and isoflavone in the genus *Reynoutria*.

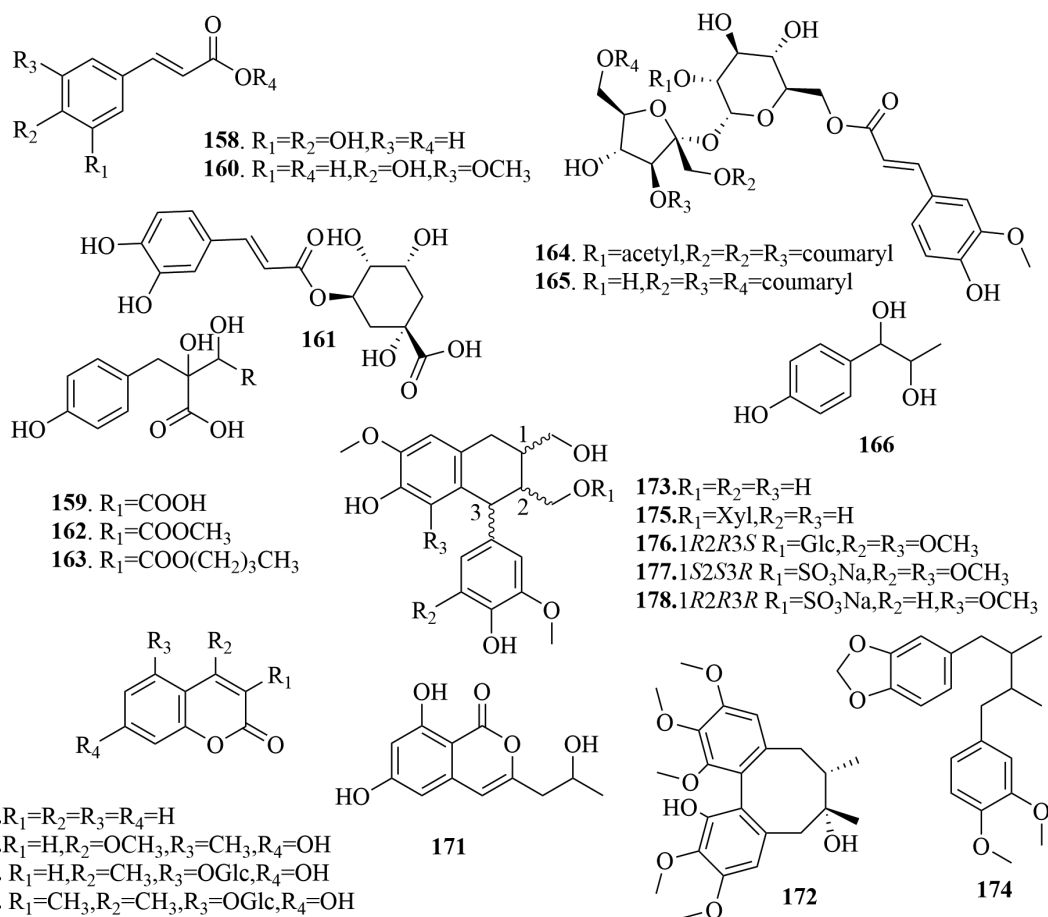


Figure 11 Structure of phenylpropanoids in the genus *Reynoutria*.

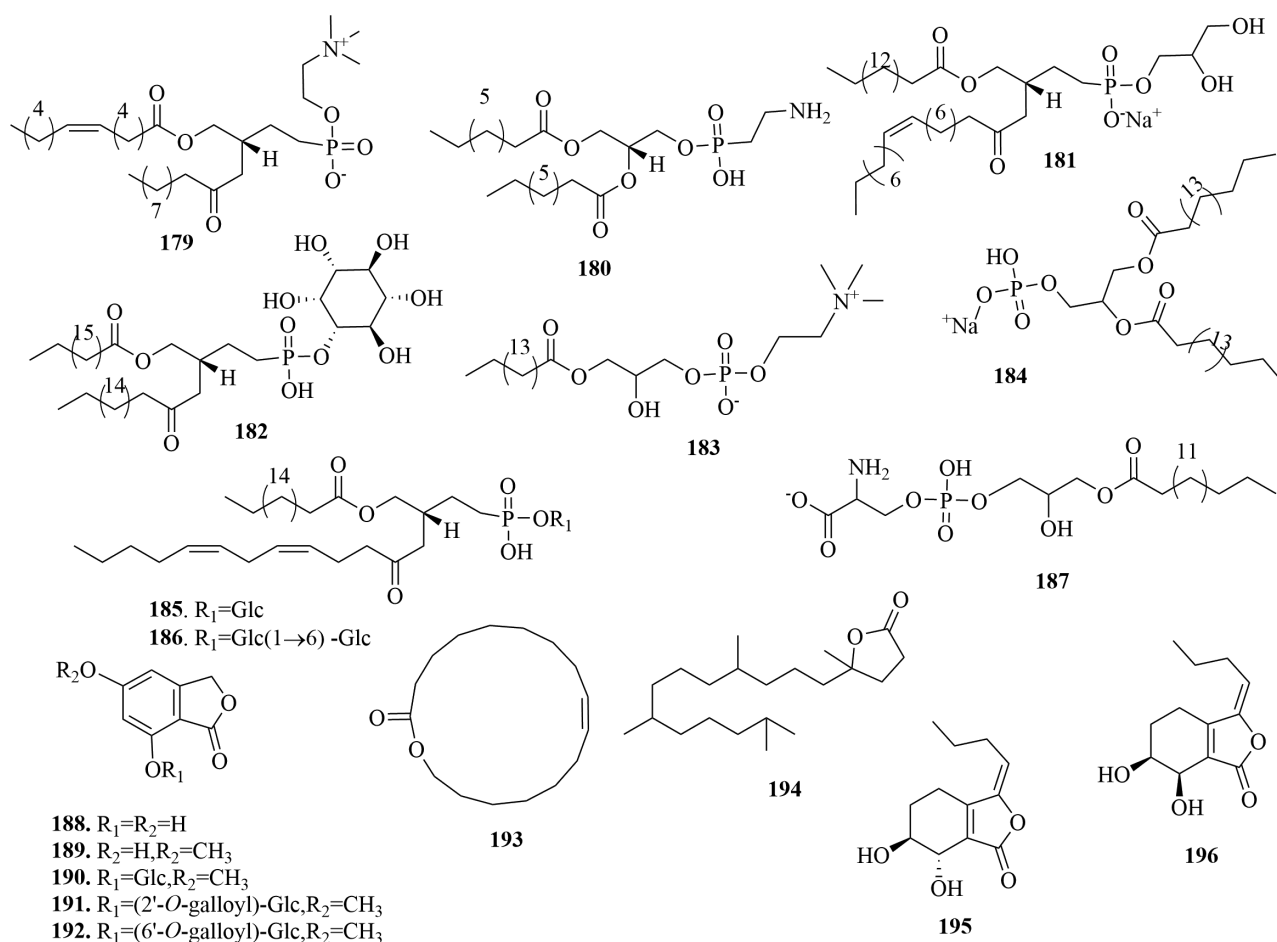


Figure 12 Structure of phospholipids and lactones in the genus *Reynoutria*.

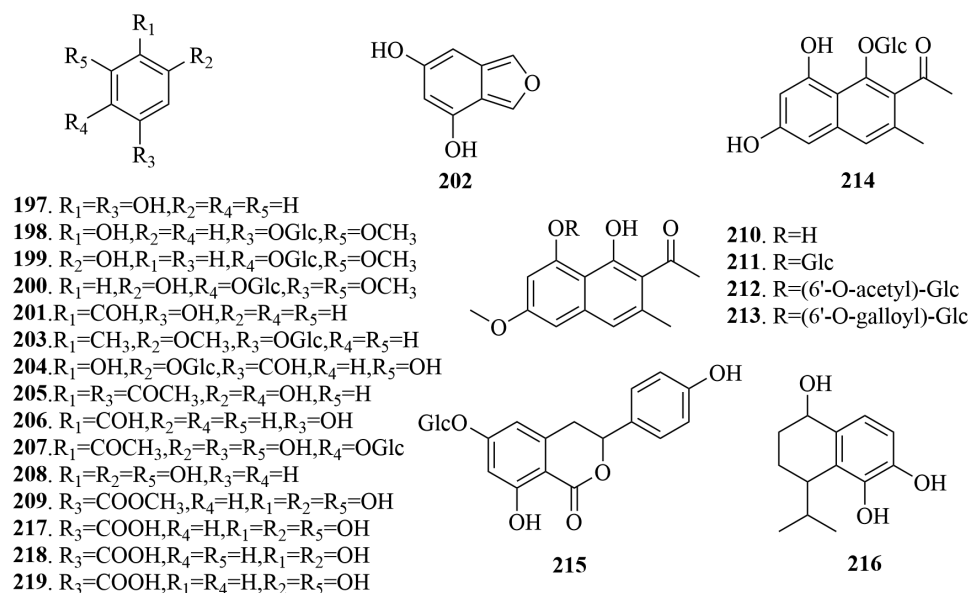
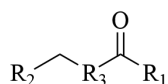


Figure 13 Structure of phenolics and phenolic acids in the genus *Reynoutria*.

the PI3K/Akt/GSK-3 β -mediated signal pathway.^[122] *In vivo*, ethanolic extract of *R. multiflora* (2 g/kg/day) improved cognitive dysfunction in diabetic rats by downregulating myosinlightchainkinase (MLCK) signaling expression.^[123]

Alzheimer's disease (AD) is the most common neurodegenerative disorder, characterized by progressive neuronal loss with amyloid β -peptide (A β) plaques. *In vivo*, TSG (120 and 240 $\mu\text{mol/kg/d}$) not only prevented learning memory impairment



- 220.** R₁=OH, R₂=COOH, R₃=CH₂
221. R₁=OH, R₂=(CH₂)₂CH₃, R₃=CH₂
222. R₁=OH, R₂=(CH₂)₁₃CH₃, R₃=CH₂
223. R₁=OH, R₂=(CH₂)₁₅CH₃, R₃=CH₂
224. R₁=OH, R₂=CHCH(CH₂)₇CH₃, R₃=(CH₂)₉
225. R₁=OCH₃, R₂=(CH₂)₅CHO, R₃=CH₂
226. R₁=OCH₃, R₂=(CH₂)₁₂CH₃, R₃=CH₂
227. R₁=OCH₃, R₂=(CH₂)₁₃CH₃, R₃=CH₂
228. R₁=OCH₃, R₂=(CH₂)₁₄CH₃, R₃=CH₂
229. R₁=OCH₃, R₂=(CH₂)₁₈CH₃, R₃=CH₂
230. R₁=OCH₃, R₂=(CH₂)₆CH₃, R₃=(CH₂)₈CH₃
231. R₁=OCH₂CH₃, R₂=(CH₂)₁₁CH₃, R₃=CH₂
232. R₁=OCH₂CH₃, R₂=(CH₂)₁₂CH₃, R₃=CH₂
233. R₁=OCH₂CH₃, R₂=(CH₂)₁₃CH₃, R₃=CH₂
234. R₁=OCH₂CH₃, R₂=(CH₂)₁₄CH₃, R₃=CH₂
235. R₁=CH₃, R₂=(CH₂)₁₆CH₃, R₃=O

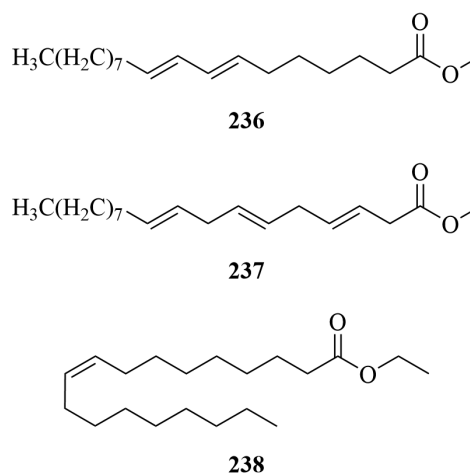


Figure 14 Structure of fatty acids in the genus *Reynoutria*.

by preventing the elevation of A β levels and amyloid plaque formation but also treated learning memory impairment by breaking down amyloid plaques.^[124] In particular, physcion-8-O- β -glucoside (5–40 mg/kg/day) significantly enhanced learning memory in A β ₁₋₄₀-induced dementia rats.^[125]

Parkinson's disease (PD) is a progressive, age-related and neurodegenerative disorder characterized by tremors, rigidity and cognitive impairment. *In vitro*, TSG (0.1 to 10 μ M) had a therapeutic effect on Parkinson's via the PI3K/Akt signal pathway against MPP⁺-induced PC12 cell damage and apoptosis.^[126] *In vivo*, TSG (20 mg/kg/day) was able to reduce MPTP-induced neurotoxicity in animal brains and treat Parkinson's disease through BDNF-Tyrosine Kinase receptor B (TrkB) and Fibroblast growth factor 2 (FGF2)-Akt signal pathways.^[127] Ethanolic extract of *R. multiflora* (400 or 800 mg/kg/day) had significant therapeutic effects on Parkinson's syndrome induced by a combination of paraquat and daidzein manganese.^[128]

Ischemic brain injury

In vitro, hexane extract from *R. multiflora* (0.1–10 μ g/ml) was found could prevent cerebral ischemic injury and significantly reduce infarct volume and neurological deficits.^[129] Emodin (10–40 mM) reduced infarct size after focal ischemia by activating the PI3K/Akt survival pathway.^[130] *In vivo*, TSG (120 mg/kg) was found to promote angiogenesis and recovery from ischemic brain injury by increasing microvessel density and upregulating the expression of CD31 in the brain,^[131] which also inhibited c-Jun N-terminal kinase (JNK) and B-cell lymphoma-2 (Bcl-2)-related apoptotic signal pathways while suppressing NF- κ B activation and reducing inducible nitric oxide synthase (iNOS) gene expression to protect neuronal cells and reduce brain infarct volume (25 μ M).^[132] Notably, it also had a significant protective effect on brain injury in ischemia-reperused mice (6 or 12 mg/kg), which ameliorated neuronal injury in the ischemic cortex and hippocampus by inhibiting NADPH oxidase 4 (NOX4), caspase-3(9), and Beclin 1 expression.^[133] Moreover, polydatin (25, 50 mg/kg/day) was effective in reducing oxygen and glucose deprivation

(OGD) damage to cultured neurons and significantly reduced cognitive impairment.^[134]

Memory improvement

TSG (42, 84 and 168 mg/kg) reduced serum levels of ROS, 2-thiobarbituric acid, NO and insulin-like growth factors-1 (IGF-1) and increased SOD and GSH-Px activity in D-galactose-induced senescent mice to improve memory capacity.^[135] Subsequent studies indicated that it improved memory capacity in mice by regulating the ERK signal pathway^[136] and the amyloid precursor protein (APP) signal pathway.^[137] Otherwise, resveratrol (25, 50 and 100 mg/kg) significantly increased the activity and expression of antioxidant enzymes and SOD to improve memory ability in mice.^[138]

Anti-virus

Emodin (1–10 μ g/ml) inhibited the infectivity of S protein-pseudotyped retroviruses on VeroE6 cells, which was a potential drug to treat coronavirus SARS.^[140] Meanwhile, it inhibited transcription and expression of EBV lysis protein (1.1, 2.1 and 4.2 μ g/ml),^[139] and inhibited Coxsackievirus B4 (CVB4)-induced apoptosis both *in vitro* and *in vivo* (EC₅₀ = 12.06 μ M). Hereby, it could be used as a potential antiviral agent for CVB4 infection.^[140] Both resveratrol and emodin were found could inhibit the growth of H3N2 and H1N1 strains and A/WSN/33 (H1N1) influenza virus through the TLR9-MYD88-IRF7 pathway (IC₅₀ = 37.3 μ M and 24.7 μ M).^[141] Resveratrol, (+)- catechin and emodin-8-O- β -D-glucoside showed an inhibitory effect on HIV-1-induced syncytium formation (EC₅₀ = 4.37, 14.4, 11.29 μ g/ml, respectively).^[142] In addition, resveratrol inhibited varicella-zoster virus (VZV) replication by limiting the synthesis of IE62 protein in a dose-dependent and reversible manner (EC₅₀ = 19 μ M).^[143] Of particular note is that resveratrol (50 μ g/mL) could inhibit the replication of herpes simplex virus-1 (HSV-1) and HSV-2 by reducing viral adherent cells and inhibiting virus reactivation.^[144] It has been found experimentally that resveratrol inhibited duck enteritis virus replication by reducing several early viral proteins essential for virus replication (IC₅₀ = 3.85 μ g/mL).^[145]

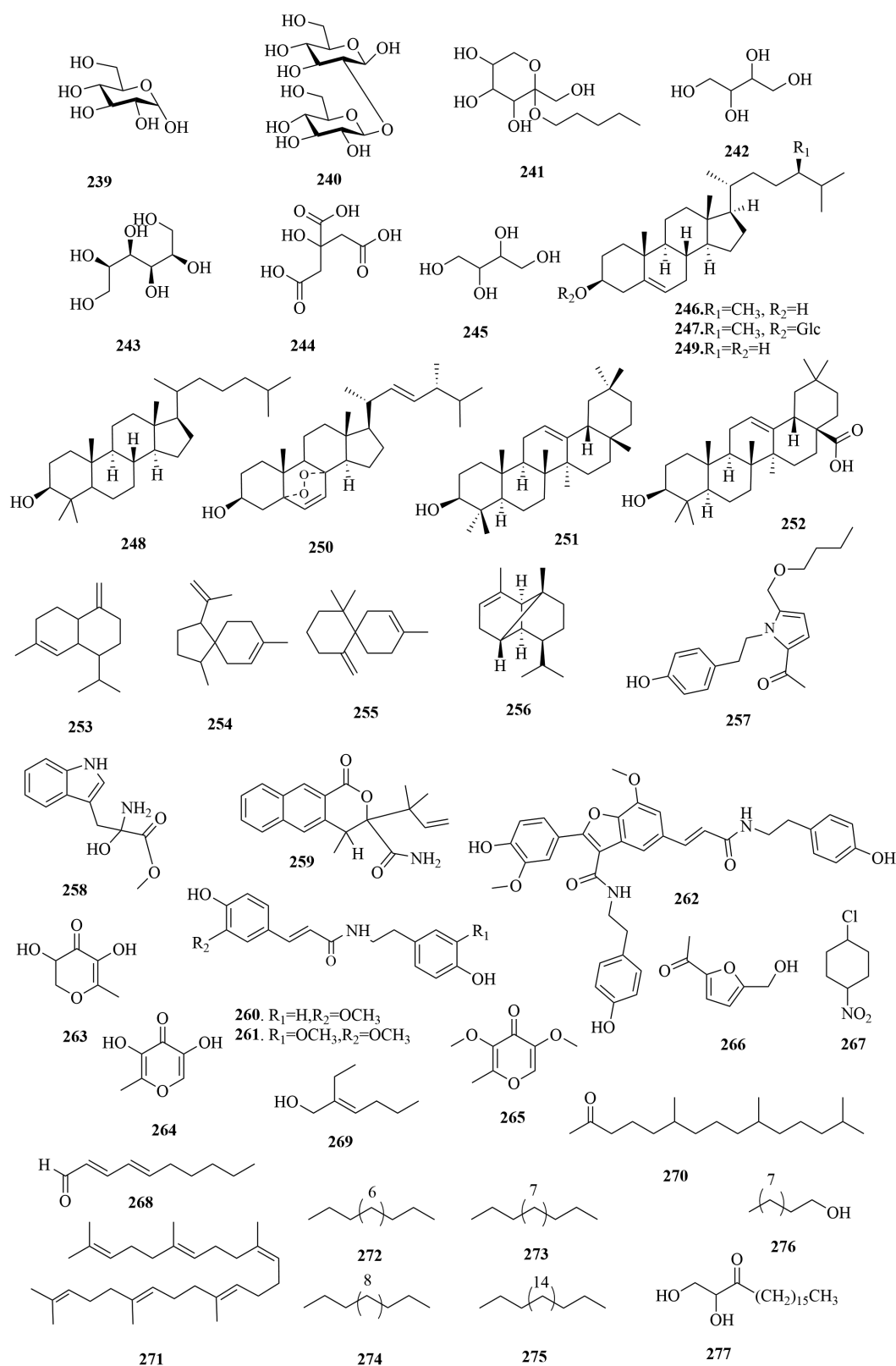


Figure 15 Structure of other compounds in the genus *Reynoutria*.

Heart protection

TSG (0.4 mM) protected against PA-induced cardiomyocyte apoptosis by stimulating miR-129-3p-targeted inhibition of Smad3 signaling,^[146] which also prevented overload stress-induced cardiac remodeling by reducing angiotensin

II, decreasing TGF- β 1 expression, inhibiting ERK 1/2 and p38 MAPK (30, 60 and 120 mg/kg/day).^[11] It is noteworthy that resveratrol (5 or 50 mg/kg/day) remodeled the heart by enhancing the activity of AMPK and silencing information regulator 1(SIRT1) in the heart and cellular

Table 2 Chemical compounds isolated and identified from the genus *Reynoutria*

No	Compounds	From	Part	Ref.
2.1 Stilbenoids				
2.1.1 2,3,5,4'-Tetrahydroxystilbene and their glycosides				
1.	2,3,5,4'-Tetrahydroxystilbene-2-O- β -D-glucoside	R1	P1	[21]
2.	2,3,5,4'-Tetrahydroxystilbene-2-O-rhamnoside	R1	P1	[22]
3.	2,3,5,4'-Tetrahydroxystilbene-2-O-xyloside	R1	P1	[23]
4.	2,3,5,4'-Tetrahydroxidene-2,3-di-O-glucoside	R1	P1	[24]
5.	2,3,5,4'-Tetrahydroxystilbene-2,4'-O-glucoside	R1	P1	[25]
6.	2,3,5,4'-Tetrahydroxystilbene-2-O- β -D-glucopyransoyl-5-O- α -D-glucoside	R1	P1	[25]
7.	2,3,5,4'-Tetrahydroxystilbene-2-O-(2''-O-acetyl)- β -D-glucoside	R1	P4	[26]
8.	2,3,5,4'-Tetrahydroxystilbene-2-O-(2''-O-galloyl)- β -D-glucoside	R1	P1	[27]
9.	2,3,5,4'-Tetrahydroxystilbene-2-O-(2''-O-feruloyl)- β -D-glucoside	R1	P4	[28]
10.	2,3,5,4'-Tetrahydroxystilbene-2-O-(2''-O-coumaryl)- β -D-glucoside	R1	P4	[28]
11.	2,3,5,4'-Tetrahydroxystilbene-2-O-(2''-O- <i>p</i> -hydroxybenzoyl)- β -D-glucoside	R1	P1	[29]
12.	2,3,5,4'-Tetrahydroxysterene-2-O-(2''-O- β -D-fructose)- β -D-glucoside	R1	P1	[25]
13.	2,3,5,4'-Tetrahydroxystilbene-2-O-(6''-O-acetyl)- β -D-glucoside	R1	P1	[29]
14.	2,3,5,4'-Tetrahydroxystilbene-2-O-(6''-O-galloyl)- β -D-glucoside	R1	P1	[27]
15.	2,3,5,4'-Tetrahydroxystilbene-2-glucosyl-(1 \rightarrow 6)- β -D-glucoside	R1	P4	[26]
16.	2,3,5,4'-Tetrahydroxystilbene-2-O-(3''-O-galloyl)- β -D-glucoside	R1	P1	[27]
17.	2,3,5,4'-Tetrahydroxystilbene-2-glucosyl-(1 \rightarrow 4)- β -D-glucoside	R1	P1	[25]
18.	<i>cis</i> -2,3,5,4'-tetrahydroxysterene-2-O-glucoside	R1	P1	[22]
19.	<i>cis</i> -2,3,5,4'-Tetrahydroxystilbene-2-glucosyl-(1 \rightarrow 6)- β -D-glucoside	R1	P1	[30]
2.1.2 resveratrol and their glycosides				
20.	Resveratrol	R1	P1	[31]
		R2	P1	[32]
		R3	P1	[33]
21.	Resveratrol-4'-O- β -D-glucoside (resveratrolside)	R1	P1	[34]
		R3	P1	[16]
22.	Resveratrol-3-O- β -D-glucoside (polydatin)	R1	P1	[31]
		R2	P1	[32]
		R3	P1	[33]
23.	Resveratrol-3-O- β -D-(2''-O-galloyl)-glucoside	R1	P1	[31]
		R2	P1	[32]
24.	Resveratrol-3-O- β -D-3-(2''-O-cinnamoyl)-glucoside	R2	P1	[32]
25.	Resveratrol-4'-O- β -D-(2''-O-galloyl)-glucopyranoside	R3	P1	[35]
26.	resveratrol-4'-O- β -D-(6''-O-galloyl)-glucopyranoside	R3	P1	[35]
27.	Rhapontin	R1	P3	[36]
28.	Isorhapontigenin	R1	P1	[37]
29.	Piceatannol	R1	P1	[37]
30.	Piceatannol glucoside	R3	P1	[38]
31.	<i>trans</i> -Stilbene glycoside sulfate 1	R3	P1	[39]
32.	<i>trans</i> -Stilbene glycoside sulfate 2	R3	P1	[39]
33.	<i>trans</i> -Stilbene glycoside sulfate 3	R3	P1	[39]
34.	<i>trans</i> -Stilbene glycoside sulfate 4	R3	P1	[39]
35.	<i>trans</i> -Stilbene glycoside sulfate 5	R3	P1	[39]
36.	<i>cis</i> -Stilbene glycoside sulfate 1	R3	P1	[39]
37.	<i>cis</i> -Stilbene glycoside sulfate 2	R3	P1	[39]
38.	<i>cis</i> -Stilbene glycoside sulfate 3	R3	P1	[39]
39.	<i>cis</i> -Stilbene glycoside sulfate 4	R3	P1	[39]
40.	<i>cis</i> -Stilbene glycoside sulfate 5	R3	P1	[39]
2.1.3 2,4,6,4'-Tetrahydroxystilbene glucoside				
41.	2,4,6,4'-Tetrahydroxystilbene-2-O- β -glucoside	R1	P1	[40]

Table 2. Continued

No	Compounds	From	Part	Ref.
2.1.4 Stilbene glycoside dimers				
42.	Multifloraiside A	R1	P1	[41]
43.	Multifloraiside B	R1	P1	[41]
44.	Multifloraiside C	R1	P1	[41]
45.	Multifloraiside D	R1	P1	[41]
46.	Multifloraiside E	R1	P1	[41]
47.	Multifloraiside F	R1	P1	[41]
48.	Multifloraiside G	R1	P1	[41]
49.	Multifloraiside H	R1	P1	[42]
50.	Multifloraiside I	R1	P1	[42]
51.	Multifloraiside J	R1	P1	[42]
52.	Multifloraiside K	R1	P1	[42]
53.	Polygonumside A	R1	P4	[43]
54.	Polygonumside B	R1	P4	[43]
55.	Polygonumside C	R1	P4	[43]
56.	Polygonumside D	R1	P4	[43]
57.	Polygonumside D	R1	P1	[44]
58.	Polygonflavanol A	R1	P1	[45]
2.2 Quinones				
2.2.1 Anthraquinones				
59.	Chrysophanol	R1	P1	[29]
		R2	P1	[46]
		R3	P1	[47]
60.	Chrysophanol-8-O-glucoside	R1	P1	[48]
		R3	P1	[49]
61.	Emodin	R1	P1	[50]
		R2	P1	[32]
		R3	P1	[33]
62.	Emodin-8-O-β-D-glucoside (anthraglycoside B)	R1	P1	[27]
		R2	P1	[46]
		R3	P1	[33]
		R4	P5	[51]
63.	Emodin-1-O-β-D-glucoside	R1	P1	[6]
64.	Emodin-8-O-(6'-O-acetyl)-glucoside	R1	P1	[52]
65.	Emodin-8-O-(6'-O-malonyl)-glucoside(emoghrelin)	R1	P1	[53]
66.	Emodin-8-O-(6'-propionyl)-glucoside	R1	P1	[54]
67.	Emodin-3-ether	R1	P1	[55]
68.	ω-Hydroxy emodin (citreorosein)	R1	P1	[29]
		R2	P1	[32]
		R3	P1	[56]
69.	ω-Hydroxy emodin-8 methyl ether (questinol)	R1	P1	[57]
		R3	P1	[58]
70.	Emodin-1-methyl ether	R1	P1	[57]
71.	Emodin-6,8-dimethyl ether	R1	P1	[52]
72.	2-Acetyl emodin	R1	P1	[29]
73.	Emodin-1,6-dimethyl ether	R1	P1	[29]
74.	Physcion	R1	P1	[27]
		R2	P1	[59]
		R3	P1	[33]
75.	Physcion-8-O-β-D-glucoside (anthraglycoside A)	R1	P1	[60]
		R2	P1	[46]
		R3	P1	[56]

Table 2. Continued

No	Compounds	From	Part	Ref.
76.	Physcion-8-O-(6'-O-acetyl)-glucoside	R1	P1	[61]
77.	Rhein	R1	P1	[62]
		R2	P1	[46]
		R3	P5	[63]
78.	Aloe-emodin	R1	P1	[29]
		R3	P5	[63]
79.	Aloe-emodin-8-O-glucoside	R1	P1	[31]
80.	Fallacinol	R1	P1	[52]
		R3	P1	[33]
81.	Digitolutein	R1	P1	[64]
82.	Polyganin A	R3	P1	[65]
83.	Polyganin B	R3	P1	[65]
84.	Xanthorin	R3	P1	[66]
85.	Isorhodoptilometrin	R3	P1	[66]
2.2.2 Naphthoquinones				
86.	2-Methoxy-6-acetyl-7-methyl-1,4-naphthoquinone	R1	P1	[67]
		R3	P1	[58]
87.	6-Methoxyl-2-acetyl-3methyl-1,4-naphthoquinone-8-O-β-D-glucoside	R1	P1	[28]
88.	7-Acetyl-2-methoxy-6-methyl-8-hydroxy-1,4-naphthoquinone	R3	P1	[68]
89.	6-Acetyl-2-methoxy-5-hydroxy-7-methyl-1,4-naphthoquinone	R3	P1	[66]
90.	6-Acetyl-5,8-dihydroxy-2-methoxy-7-methyl-1,4-naphthoquinone	R3	P1	[66]
91.	Cuspidatumin C	R3	P1	[66]
92.	3-Acetyl-5-hydroxy-7-methoxy-2-methyl-1,4-naphthoquinone	R3	P1	[66]
93.	cuspidatumin A	R3	P1	[68]
2.2.3 Benzoquinones				
94.	Phylloquinone B	R3	P1	[69]
95.	Phylloquinone C	R3	P1	[69]
2.2.4 Di-anthraquinones				
96.	Polygonumnlolide A1	R1	P1	[70]
97.	Polygonumnlolide A2	R1	P1	[70]
98.	Polygonumnlolide A3	R1	P1	[70]
99.	Polygonumnlolide A4	R1	P1	[70]
100.	Polygonumnlolide B1	R1	P1	[70]
101.	Polygonumnlolide B2	R1	P1	[70]
102.	Polygonumnlolide B3	R1	P1	[70]
103.	Polygonumnlolide C1	R1	P1	[71]
104.	Polygonumnlolide C2	R1	P1	[71]
105.	Polygonumnlolide C3	R1	P1	[71]
106.	Polygonumnlolide C4	R1	P1	[71]
107.	Polygonumnlolide E	R1	P4	[44]
108.	<i>trans</i> -Emodin dianthrones	R1	P1	[71]
109.	<i>cis</i> -Emodin dianthrones	R1	P1	[71]
2.3 Flavonoids				
2.3.1 Chromones				
110.	Noreugenin	R1	P3	[36]
111.	2,5-Dimethyl-7-hydroxychromone	R1	P1	[67]
		R2	P1	[46]
		R3	P1	[58]
112.	2-(2'-Hydroxypropyl)-5-methylchromogenketone-7-O-β-D-glucopyranoside	R1	P1	[67]
113.	(<i>s</i>)-2-(2-hydroxypropyl)-5-methyl-7-hydroxychromogenketone-7-O-α-L-fucosyl (1→2)-β-D-glucoside	R1	P1	[4]
114.	5-Carboxymethyl-7-hydroxy-2-methyl chromone	R1	P1	[48]
		R2	P1	[46]

Table 2. Continued

No	Compounds	From	Part	Ref.
115.	2-Methyl-5-hydroxymethyl-7-hydroxychromone	R2	P1	[46]
116.	2-Methyl-5-methylcarboxymethyl-7-hydroxychromone	R2	P1	[46]
117.	2-Methyl-5-carboxylicacid-7-hydroxy-chromone	R2	P1	[46]
118.	2-(2'-Hydroxypropyl)-5-methyl-7-hydroxychromone	R1	P2	[72]
119.	2,5-Dimethyl-7-hydroxy-chromone-7-O-β-D-glucopyranoside	R1	P2	[72]
		R2	P1	[46]
120.	Noreugenin-7-O-β-D-glucopyranoside	R1	P2	[72]
121.	Polygonumside E	R1	P1	[67]
122.	Polygonimitin B	R1	P1	[24]
2.3.2 Flavones				
123.	Tricin	R1	P1	[67]
124.	Apigenin	R3	P5	[63]
125.	Tricin-7-O-β-D-glucoside	R1	P4	[5]
126.	Vitexin	R1	P3	[36]
127.	Isoorientin	R1	P1	[73]
128.	Kaempferol	R1	P1	[29]
		R3	P1	[47]
129.	Quercetin	R1	P1	[31]
		R3	P5	[63]
		R4	P5	[51]
130.	Isoquercetin (querctin-3-O-β-D-glucopyranoside)	R3	P1	[66]
		R4	P5	[51]
131.	Hyperoside	R1	P3	[36]
			P1	[74]
		R3	P1	[66]
132.	Rutin	R1	P3	[36]
		R3	P5	[63]
133.	Quercetin-3-O-β-D-arabinoside	R1	P1	[74]
		R3	P1	[68]
134.	Querctin-3-O-β-D-rhamnoside	R3	P1	[66]
135.	Querctin-3-O-β-D-xyloside (reynoutrin)	R3	P1	[66]
136.	Icaritin	R1	P1	[6]
137.	Kaempferitrin	R2	P1	[6]
138.	Annulatin-3'-O-β-D-xyloside	R2	P1	[6]
139.	Luteolin-7-O-glucoside	R3	P1	[66]
2.3.3 Flavanones				
140.	(+)-Catechin (C)	R1	P1	[75]
		R3	P1	[69]
		R4	P3	[76]
		R5	P3	[76]
141.	(+)-Catechin-5-O-β-D-glucopyranoside	R3	P1	[77]
142.	Epicatechin (EC)	R1	P1	[75]
		R3	P1	[47]
		R4	P3	[76]
		R5	P3	[76]
143.	Gallocatechin(GC)	R1	P1	[75]
144.	Epigallocatechin (EGC)	R1	P1	[75]
145.	Catechin gallic acid (CG)	R1	P1	[75]
146.	Epicatechin gallate (ECG)	R1	P1	[75]
		R4	P3	[76]
		R5	P3	[76]
147.	Gallocatechin gallate (GCG)	R1	P1	[75]
148.	Epigallocatechin gallate (EGCG)	R1	P1	[75]

Table 2. Continued

No	Compounds	From	Part	Ref.
149.	Proanthocyanidin	R1	P1	[78]
150.	Proanthocyanidin B1	R1	P1	[78]
		R4	P3	[76]
151.	Proanthocyanidin B2	R1	P1	[78]
		R4	P3	[76]
		R5	P3	[76]
152.	Proanthocyanidin C1	R4	P3	[76]
153.	3-O-galloyl-procyanidin B-2	R1	P1	[79]
154.	3,3'-di-O-galloyl-procyanidin B-2	R1	P1	[79]
155.	Polygonflavanol A	R1	P1	[45]
2.3.4 Isoflavone				
156.	Genistin	R1	P2	[72]
		R3	P5	[63]
2.3.5 Flavonone				
157.	Hesperetin	R3	P5	[63]
2.4 Phenylpropanoids				
2.4.1 Simple phenylpropanoids				
158.	Caffeic acid	R1	P2	[72]
		R3	P1	[69]
159.	Piscidic acid	R2	P1	[6]
160.	Ferulic acid	R3	P1	[69]
161.	Chlorogenic acid	R3	P1	[69]
162.	2-Methyl-(4-hydroxybenzyl)-tartrate	R2	P1	[6]
163.	2-Monobutyl-(4-hydroxybenzyl)-tartrate	R2	P1	[6]
164.	Vanicosides A	R4	P6	[80]
165.	Vanicosides B	R4	P6	[80]
166.	1,2-Propanediol-1-(4-hydroxy-phenyl)	R1	P1	[30]
2.4.2 Coumarins				
167.	Coumarin	R3	P1	[68]
168.	7-Hydroxy-4-methoxy-5-methylcoumarin	R3	P1	[58]
169.	7-Hydroxy-4-methylcoumarin-5-O-glucoside	R1	P1	[28]
170.	7-Hydroxy-3,4-dim-methyl-coumarin-5-O-glucoside	R1	P1	[28]
171.	Polyisocoumarin	R3	P1	[81]
2.4.3 Lignans				
172.	Schizandrin	R1	P4	[82]
173.	Isolariciresinol	R2	P1	[46]
174.	5-[4-(3,4-dimethoxyphenyl)-2,3-dimethylbutyl]-1,3-benzodioxole	R2	P1	[46]
175.	Isolariciresinol-9-O-β-D-xylopyranoside	R2	P1	[46]
176.	(+)-Lyoniresinol-3-α-O-β-D-glucopyranoside	R1	P1	[30]
177.	Sodium(-)-lyoniresinol-2a-sulfate	R3	P1	[77]
178.	Sodium(+)-isolaricireinol-2a-sulfate	R3	P1	[77]
2.5 Phospholipids				
179.	Phosphatidylcholine (PC)	R1	P4	[82]
180.	Phosphatidylethanolamine (PE)	R1	P1	[83]
181.	Phosphatidylglycerol (PG)	R1	P1	[83]
182.	Phosphatidylinositol (PI)	R1	P1	[83]
183.	Iysophosphatidylcholine (LPC)	R1	P1	[84]
184.	Phosphatidylserine	R1	P1	[84]
185.	1-O-Stearoyl-2-O-Δ ^{4,7} -dodecenoyl-3-O-phosphatidicacid-O-β-D-glucoside	R1	P4	[28]
186.	1-O-stearoyl-2-O-Δ ^{4,7} -dodecenoyl-3-O-phosphatidicacid-O-(6''-O-α-D-2-glucose)-β-D-glucoside	R1	P4	[28]
187.	Phosphatidic acid	R1	P1	[83]

Table 2. Continued

No	Compounds	From	Part	Ref.
2.6 Lactones				
188.	5,7-Dihydroxy-isobenzofuran	R2 R3	P1 P1	[46] [56]
189.	5-Methoxy-7-hydroxy-isobenzofuran	R2	P1	[46]
190.	5-Methoxy-isobenzofuran-7-O- β -D-glucoside	R2	P1	[46]
191.	Polyphthaliside A	R3	P1	[81]
192.	Polyphthaliside B	R3	P1	[81]
193.	Ambrettolide	R3	P1	[68]
194.	4,8,12,16-Tetramethylheptadecan-4-olide	R1	P4	[85]
195.	<i>cis</i> -E-3-butylidene-4,5,6,7-tetrahydro-6,7-dihydroxy-l(3H)-isobenzofuranone	R1	P1	[40]
196.	<i>trans</i> -E-3-butylidene-4,5,6,7-tetrahydro-6,7-dihydroxy-l(3H)-isobenzofuranone	R1	P1	[40]
2.7 Phenolics and phenolic acids				
2.7.1 Phenolics				
197.	1,4-Benzenediol	R1	P4	[57]
198.	Tachioside	R3	P1	[69]
199.	Isotachioside	R3	P1	[69]
200.	2,6-Dimethoxy-phydroquinone-1-O- β -D-glucopyranoside	R3	P1	[66]
201.	4-Hydroxyacetophenone	R3	P5	[63]
202.	5,7-Dihydroxyisobenzofuran	R3	P1	[56]
203.	2-(Hydroxymethyl)-6-(3-methoxy-4-methylphenoxy)tetrahydro-2H-pyran-3,4,5-triol	R1	P1	[86]
204.	1-(3-O- β -D-glucopyranosyl-4,5-dihydroxy-phenyl)-acetophenone	R3	P1	[69]
205.	2,5-Diacetylhydroquinone	R2	P1	[46]
206.	<i>p</i> -Hydroxybenzaldehyde	R1	P4	[57]
207.	2,3,4,6-Tetrahydroxyacetophenone-3-O- β -D-glucoside	R1	P1	[74]
208.	Pyrogallol	R1	P1	[67]
209.	Methylgallate	R1	P1	[54]
210.	Torachryson	R3	P1	[66]
211.	Torachryson-8-O- β -D-glucoside	R2 R3	P1 P1	[6] [69]
212.	Torachryson-8-O-(6'-galloyl)- β -D-glucoside	R2	P1	[6]
213.	Torachryson-8-O-(6'-O-acetyl)- β -D-glucoside	R2 R3	P1 P1	[32] [69]
214.	6-Hydroxymusizin-8-O- β -D-glucoside	R2	P1	[32]
215.	Thunberginol C-6-O- β -D-glucopyranoside	R1	P1	[30]
216.	5,6,7,8-Tetrahydro-2,5-dimethyl-8-(1-methyl-ethyl)-1-naphthalenol	R1	P4	[85]
2.7.2 Phenolic acids				
217.	Gallic acid	R1 R2 R3	P4 P1 P1	[87] [6] [69]
218.	Protocatechuic acid	R3	P1	[68]
219.	2,6-Dihydroxy-benzoic acid	R1	P1	[30]
2.8 Fatty acids				
220.	Succinic acid	R2	P1	[6]
221.	Hexanoic acid	R1	P4	[85]
222.	Palmitic acid	R3	P1	[69]
223.	Stearic acid	R3	P1	[69]
224.	Arachidonic acid	R3	P1	[69]
225.	Nonanoic acid,9-oxo,methyl ester	R1	P4	[85]
226.	Hexadecanoic acid methyl ester	R1	P4	[85]
227.	Heptadecanoic acid methyl ester	R1	P4	[85]
228.	Octadecanoic acid methyl ester	R1	P4	[85]
229.	Docosanoic acid methyl ester	R1	P4	[85]

Table 2. Continued

No	Compounds	From	Part	Ref.
230.	10-octadecenoic acid methyl ester	R1	P4	[85]
231.	Tetradecanoic acid ethyl ester	R1	P4	[85]
232.	Hexadecanoic acid ethyl ester	R1	P4	[85]
233.	Heptadecanoic acid ethyl ester	R1	P4	[85]
234.	Octadecanoic acid ethyl ester	R1	P4	[85]
235.	Acetic acid octadecyl ester	R1	P4	[85]
236.	9,11-Octadecadienoic acid methyl ester	R1	P4	[85]
237.	(Z,Z,Z)-9,12,15-octadecatrienoic acid methyl ester	R1	P4	[85]
238.	Ethyl oleate	R1	P4	[85]
2.9 Saccharides				
239.	α -D-glucose	R2	P1	[6]
240.	Inotodisaccharide	R2	P1	[6]
241.	<i>n</i> -Butyl- β -D-fructopyranoside	R2	P1	[6]
2.10 Polyols				
242.	Erythritol	R2	P1	[6]
243.	D-mannitol	R3	P1	[47]
244.	Citric acid	R3	P1	[47]
245.	(1S,2R,3R,4S)-4-(hydroxymethyl)-4-pentylcyclopentane-1,2,3-triol	R1	P1	[27]
2.11 Steroids				
246.	β -Sitosterol	R2	P1	[6]
		R3	P5	[63]
247.	Daucosterol	R2	P1	[6]
		R3	P5	[63]
		R4	P5	[51]
248.	Dammaran-3 β -ol	R4	P5	[51]
249.	Campesterol	R4	P5	[51]
250.	Ergosterol peroxide	R4	P5	[51]
2.12 Terpenoids				
251.	β -Amyrin	R1	P3	[36]
		R4	P5	[51]
252.	Oleanolic acid	R3	P1	[68]
253.	1,2,3,4,4a,5,6,8a-Octahydro-7-methyl-4-methyl naphthalene	R1	P4	[85]
254.	1,8-Dimethyl-4-(1-methyl-2-ethenyl)-spiroene	R1	P4	[85]
255.	3,7,7-Trimethyl-11-methylenespiro[5.5]undec-2-ene	R1	P4	[85]
256.	Copaene	R1	P4	[85]
2.13 Alkaloids				
257.	Pyrrolezanthine-6-monobutyl-ether	R2	P1	[6]
258.	Indole-3-(L- α -amino- <i>a</i> -hydroxypropionic acid) -methyl ester	R1	P1	[30]
259.	Polygonimitin A	R1	P1	[30]
260.	<i>n</i> -Trans-feruloyl tyramine	R1	P1	[67]
261.	<i>n</i> -Trans-feruloyl-3'-O-methyldopamine	R1	P1	[62]
262.	(<i>E</i>)-2-(4-hydroxy-3-methoxyphenyl)-3-[N-2-(4-hydroxyphenyl)ethyl]carbamoyl-5-[N-2-(4-hydroxyphenyl)ethyl]carbamoyl-7-methoxybenzofuran	R1	P1	[88][89]
2.14 Miscellaneous compounds				
263.	2,3-Dihydro-3,5-dihydroxy-6-methyl-4-H-pyranone(DDMP)	R1	P4	[57]
264.	5-Hydroxymaltol	R1	P4	[57]
265.	Zanthopyranone	R2	P1	[46]
266.	5-Hydroxymethyl-furfura	R1	P4	[57]
267.	1-Chloro-4-mitro-benzene	R1	P4	[85]
268.	(<i>E,E</i>)-2,4-decedienal	R1	P4	[85]
269.	2-Ethyl-2-hexenlol	R1	P4	[85]
270.	6,10,14-Trimethyl-2-pentadecanone	R1	P4	[85]
271.	Squalene	R1	P4	[85]

Table 2. Continued

No	Compounds	From	Part	Ref.
272.	dodecane	R1	P2	[72]
273.	Tridecane	R1	P2	[72]
274.	Tetradecane	R1	P2	[72]
275.	Eicoeane	R1	P4	[85]
276.	1-Decanol	R4	P5	[51]
277.	1,2-Dihydroxy nonadecane -3	R1	P4	[85]

R1: *R. multiflora*; R2: *R. ciliinervis*; R3: *R. japonica*; R4: *R. sachalinensis*; R5: *Reynoutria × bohémica*
 P1: Tuberous roots; P2: stems; P3: leaves; P4: processed roots; P5: flowers; P6: rhizomes

autophagy.^[147] Polydatin (100, 200 mg/kg/day) significantly limited the infarct size through activation of protein kinase C-ATP-sensitive potassium channel (PKC-KATP)-dependent signaling and anti-oxidative stress mechanisms,^[148] which also had an attenuating effect on ventricular remodeling.^[149] *In vivo and vitro*, TSG inhibited the production of reactive oxygen species and elevated Bcl-2 protein levels to protect the heart from doxorubicin (DOX)-induced effects.^[150] A study has shown that resveratrol at lower doses still ensured the survival of cardiomyocytes through autophagy of the mTOR-Rictor pathway (0.1 and 1 mM in cells and 2.5 mg/kg/day in rats).^[151]

Liver protection

In vitro, emodin (20–160 μM) protected against hepatocyte apoptosis by inhibiting the PI3K/AKT/mTOR signal pathway.^[152] *In vivo*, polydatin (50 or 100 mg/kg) inhibited liver tissue inflammation in carbon tetrachloride injured mice by lowering alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and restoring the balance of antioxidants in liver tissue.^[153] Meanwhile, polydatin (6.25, 12.5 and 25 μg/ml) reduced the expression of genes related to alcohol and lipid metabolism and inhibited oxidative stress in the liver. Notably, it significantly upregulated the expression of DNA damage-related genes to reduce hepatocyte apoptosis,^[154] and attenuate nonalcoholic fatty liver disease (30 or 90 mg/kg) by reducing the expression of SREBP-1c and genes involved in adipogenesis, including fatty acid synthase (FAS) and stearoyl-CoA desaturase 1 (SCD1).^[155] TSG (100 or 300 mg/kg) significantly reduced CCl₄-induced liver injury in rats by inhibiting Smad and ERK signal pathways,^[156] which also protected the liver from injury by inducing hepatic autophagic cell death by activating PI3K/Akt and Erk pathways (100 or 200 mg/kg).^[157]

Anti-bacterial

Emodin (10 μg/ml) significantly inhibited the growth and infection of *Vibrio traumaticus* and the combination with other antibiotics may help patients to treat *Vibrio traumaticus* sepsis.^[158] Resveratrol was found to have a minimum inhibitory concentration (MIC) of 50 μg/ml against *Mycobacterium avium* wax,^[159] the MIC against *Mycobacterium pubescens* was 64 μg/ml,^[160] *H. pylori* was 25 μg/ml,^[161] *Vibrio cholerae* was 60 μg/ml,^[162] *Campylobacter coli* was 50 μg/ml,^[163] and Lactic acid bacteria was 50 μg/ml.^[164]

Anti-fungal

Emodin inhibited phosphorylation induced by the protein kinase CK2 and showed resistance to *Candida* with MIC and

minimal fungicidal concentration (MFC) values between 12.5 and 200 μg/ml. Notably, even at low concentrations, it was effective in preventing the formation of mycelium.^[165] Resveratrol had a toxic effect on dormant gray mold conidia.^[166] The inhibitory activity of resveratrol against *Trichophyton rubrum*, *Trichophyton flocculentum* epidermidis, and *Microsporum gypsum* was about 25–50 μg/ml,^[167] against *Candida albicans*, *Saccharomyces cerevisiae* and *Serratia marcescens* was 10–20 μg/ml.^[168]

Hyperglycemia

Proanthocyanidins isolated from *R. multiflora* were found to display potent α-amylase and moderate α-glucosidase inhibitory activity with an acarbose equivalence (AE) value of 1,954.7 μmol AE/g and 211.1 μmol AE/g, respectively.^[169] *Cis*-TSG was more effective than *trans*-TSG in terms of hypoglycemic effect and improvement of glucose intolerance and insulin resistance. In HepG2 cells, *cis*-THSG also showed stronger Phosphoenolpyruvate carboxykinase (PEPCK) transcriptional repression to reduce blood glucose than *trans*-THSG.^[170]

Obesity

R. multiflora extract (0.46 mg/ml) had a strong inhibitory effect on fatty acid synthase FAS can be used to prevent obesity.^[171] Meanwhile, *R. multiflora* root ethanol extract (5 or 10 μg/ml) prevented obesity by inhibiting adipocyte differentiation in 3T3-L1 cells and stimulating the expression of genes for lipolysis and fatty acid oxidation and brown fat-specific genes in white adipose tissue.^[172]

Bone protection

TSG (10⁻³, 10⁻⁴ and 10⁻⁵ mg/ml) treated osteoporosis by activating the PI3K/Akt pathway, which promotes proliferation and differentiation of MC3T3-E1 cells.^[173] Similarly, *trans*-resveratrol (0.7 mg/kg) increased epiphyseal bone density and inhibited the decrease of bone calcium content in bilateral ovariectomies (OVX) rats, which had a protective effect against estrogen deficiency-induced bone loss.^[174]

Promotes hair growth

In vitro, *R. multiflora* extract (10 or 100 μg/ml) could promote hair growth by prolonging the initial phase of hair growth and activating follicle stem cells to delay hair degeneration.^[175] It was found that *R. multiflora* water extract (0.01 mg/ml) was able to reduce the accumulation of ROS in cells, protect cells from hydrogen peroxide and improve pigmentation of isolated human hair follicles.^[176] Studies showed that fermented water extract of *R. multiflora* leaves (4.7 mg/12 cm²) could

induce hair growth in resting hair follicles by upregulating Shh and β -catenin expression.^[177] Meanwhile, TSG (200 μ M) had a good hair regrowth effect on hair loss, which may be achieved by inhibiting p53, Fas, and Bcl2-Associated X (Bax)-induced apoptosis.^[178]

Toxicity

Chrysophanol-8-O-glucoside had strong hepatotoxicity which can increase LDH leakage and ROS, and decrease GSH and MMP in L-02 hepatocytes.^[179] In vitro neurotoxicity experiments showed that *R. japonica* water extract (300 and 400 μ g/ml) had general toxicity and neurotoxicity on hippocampal neurons and astrocyte cells, respectively.^[180] Experimental evidence indicated that in the setting of hepatic immune activation, *cis*-2,3,5,4'-tetrahydroxystilbene-2-O- β -D-glucoside was a key factor in the pathogenesis of the idiosyncratic hepatotoxicity of *R. multiflora*.^[181] In addition, Aloe-emodin could cause zebrafish liver lesions by increasing the mRNA and protein expression levels of pro-inflammatory and pro-apoptotic targets in NF- κ B and P53 pathways and pathological sections.^[182] All the pharmacological effects of this genus are summarized in [Supplementary Table S1](#).

Discussion and Further Perceptives

This review summarized current research development regarding the traditional uses, phytochemistry and pharmacology of genus *Reynoutria*. More than 277 compounds have been isolated and identified from this genus. Meanwhile, modern pharmacological research revealed *Reynoutria* plants have significant pharmacological properties including anti-cancer, anti-atherosclerotic, anti-inflammatory and neuroprotective. Regardless, there are still several aspects that need to be concerned about the further development of the genus *Reynoutria*.

First, *Fallopia multiflora* and *Fallopia multiflora* var. *ciliinerve* have been now reclassified as a member of the genus *Reynoutria*, just as *R. japonica* was divided from the genus *Fallopia* to the genus *Reynoutria*. Now, they were formally called *Reynoutria multiflora* (thumb.) Moldenke and *Reynoutria ciliinervis* (Nakai) Moldenke, respectively. However, in Asian countries such as China, they are still regarded as *Fallopia* plants, which is urgent to be corrected.

Second, the current phytochemical studies on the genus *Reynoutria* focus on *R. multiflora* and *R. japonica*. Other *Reynoutria* plants are regarded as invasive plants in Europe and America, and their phytochemical and biological activities have not yet been comprehensively investigated.

Third, 277 compounds have been reported from genus the *Reynoutria*, including 58 stilbenoids, 51 quinones, 48 flavonoids, 21 phenylpropanoids, 9 phospholipids, 9 lactones, 23 phenolics and phenolic acids, 19 fatty acids, and 39 other compounds. Among them, stilbenoids are the main active compounds, which have a variety of pharmacology activities. 2,3,5,4'-tetrahydroxystilbene-2-O- β -D-glucoside showed excellent activity in anti-aging, anti-inflammatory, hepatoprotective and free radical scavenging.^[183] Resveratrol has significant anti-infective, antiviral, and cardiovascular protective effects.^[184] More stilbenoids with various activities need to be found in this genus. Of course, it cannot be ignored that monomeric compounds with outstanding pharmacological activities can be considered the source of new drugs with excellent therapeutic effects.

Finally, *Reynoutria* plants were widely used in the treatment of chronic hepatopathy, but it was noteworthy that they were reported to have hepatotoxicity as well. For instance, pang et al found that the high dosage of *R. multiflora* had either an injuring effect on normal rats or a therapeutic effect on the rats with chronic liver injury.^[185] Therefore, it is still necessary to further study the material basis and mechanism of hepatotoxicity to provide a scientific basis for clinical medication.

Conclusion

Reynoutria is a genus in the family Polygonaceae, many species of which have been used in traditional Chinese medicines or folk medicines to treat various diseases. This review summarized all the compounds of genus *Reynoutria*, including stilbenoids, quinones, flavonoids and so on. Stilbenoids and quinones were generally considered major bioactive ingredients in *Reynoutria*, exhibiting various important qualities. In addition, pharmacological studies showed that compounds and extracts isolated from *Reynoutria* plants possess a wide range of pharmacological activities, such as anti-cancer, anti-atherosclerotic, anti-inflammatory and neuroprotective. In short, as a source of traditional folk medicine, *Reynoutria* plants are widely used in medicine. Therefore, we believe it's necessary to review this genus, which will help to gain a greater understanding and appreciation of genus *Reynoutria*.

Supplementary Material

Supplementary data are available at *Journal of Pharmacy and Pharmacology* online.

Author Contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Data Availability

The underlying data supporting the study are available within the article.

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