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Therapeutic Potential of Phenylethanoid Glycosides: A Systematic Review

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Conflict of Interest

The authors declare no conflict of interest.

Abstract

Phenylethanoid glycosides (PhGs) are generally water-soluble phenolic compounds that occur in many medicinal plants. Until June 2020, more than 572 PhGs have been isolated and identified. PhGs possess antioxidant, neuroprotective, anti-inflammatory, antibacterial, antiviral, antidiabetic, anticancer, and anti-obesity properties. Despite these promising benefits, PhGs have failed to fulfill their therapeutic applications due to their poor bioavailability. The attempts to understand their metabolic pathways to improve their bioavailability are investigated. In this review article, we will first summarize the number of PhGs compounds which is not accurate in the literature. The latest information on the biological activities, structure-activity relationships, mechanisms and especially the clinical applications of PhGs will be reviewed. The bioavailability of PhGs will be summarized and factors leading to the low bioavailability will be analyzed. Recent advances in methods such as bioenhancers and nanotechnology to improve the bioavailability of PhGs are also summarized. The existing scientific gaps of PhGs in knowledge are also discussed, highlighting research directions in the future.

Keywords: Phenylethanoid glycosides; Bioavailability; Verbascoside; Salidroside; Echinacoside

1. Introduction

Phenylethanoid glycosides (PhGs) are generally water-soluble phenolic compounds that occur in many medicinal plants. PhGs have been isolated from the roots, stems, bark, leaves, flowers, fruits and seeds of medical plants, as well as from suspension cell cultures, callus tissues and hairy roots cultures. They are also found in various plant-based foods such as edible flowers and tea. However, their accumulations in each plant organ may vary considerably[1-3]. The main PhGs are reported from the families Acanthaceae, Berberidaceae, Asteraceae, Gesneriaceae, Lamiaceae, Loganiaceae, Magnoliaceae, Oleaceae, Orobanchaceae, Plantaginaceae, Portulacaceae, Rosaceae, Scrophulariaceae, and Verbenaceae[4]. For example, a total of 69, 51, 21 and 16 PhGs have been isolated from *Cistanche herba*[5], *Forsythiae fructus*[6], *Magnoliae officinalis*[7] and *Houttuynia cordata*[8], respectively. Verbascoside (also known as acteoside), one of the representative PhGs, is widely distributed in the family Lamiaceae，Plantaginaceae, Scrophulariaceae, and Orobanchaceae[9]. In1994, Jiménez and Riguera summarized the structures and biological activities of 155 PhGs reported before 1992[2]. In 2008, Fu et al. provided an overview in the advances on 190 new PhGs isolated from 1997 to 2007[10]. The detailed information of 116 new PhGs identified during 2009-2016 was given in 2016[3]. In the present review, we summarized the 111 PhGs[11-56] that have not been reviewed previously (1993-1997, 2007-2009 and 2016-present) in Table 1 and Table 2. The latest new PhGs (Ginkgoside C and D) was published on 16 June 2020. Up to 572 PhGs were identified from nature until June 2020. These 572 PhGs are distributed in 21 orders and 35 families of the plant kingdom (Figure 1). It should be noted that some PhGs identified were not published in English. Thus, the actual number identified must be over 572.

In general, the basic structure of PhGs consists of a hydroxyphenylethyl unit as an aglycone which is attached to a sugar moiety mostly a β-D-glucopyranose through a glycosidic bond at the C-1 site. In most cases, the glucose moiety is esterified with a hydroxycinnamic acid derivative such as caffeic acid, coumaric acid, cinnamic acid, and ferulic acid. Rhamnose, xylose, arabinose, allose, galactose, and apiose, among others, may also be attached to the glucose residue (Figure 2, Table 1 and 2). The diversity of sugar and hydroxyphenylethyl moieties make the plentiful variation of PhGs. Generally, the number of sugars ranges from one to three. However, four-sugar and five-sugar residues are also found occasionally. According to the number of the sugars bonded to hydroxyphenylethyl moieties, PhGs can be classified into monosaccharidic PhGs, dissaccharidic PhGs, trisaccharidic PhGs, tetrasaccharidic PhGs, and pentasaccharidic PhGs[4]. To date, there are 10 tetrasaccharidic PhGs reported, namely, magnolosides C[57], ballotetroside[58], trichosanthoside B[59], marruboside[60], velutinosides I[61], velutinosides II[61], lunariifolioside[62],

raduloside[63], barlerinoside[64], and poliumoside B[65]. Only one pentasaccharidic PhGs named yulanoside A from *M. salicifolia* was reported in 2015[66]. The representative chemical structures of monosaccharidic PhGs, dissaccharidic PhGs, trisaccharidic PhGs, tetrasaccharidic PhGs, and pentasaccharidic PhGs are shown in Figure 2.

Most purified PhGs are white, buff or yellow amorphous powders with high polarity. They are soluble in polar solvents but insoluble in non-polar organic solvents[67]. As the characteristics of the strong ultraviolet (UV) absorption in PhGs, it is easy to monitor these compounds by UV spectrophotometer. The specific UV spectra of each PhGs can also serve as an index to deduce the structure. For example, the UV absorption peaks of verbascoside and isoverbascoside are 232, 246, 289, 332 nm, and 232, 246, 286, 328 nm, respectively[68]. And that of echinacoside are 236, 288, 330 nm[69].

PhGs and the extracts rich in PhGs exhibited various benefits, such as antioxidant activity, neuroprotective effect, anti-inflammatory activity, antibacterial activity, antivirus activity, anti-diabetic activity, anti-cancer activity, and anti-obesity activity[3, 9]. Figure 3 shows the number of papers and times cited of papers indexed in the Web of Science related to "PhGs", illustrating a significant increase in publication in this area. Although over 572 PhGs have been isolated and identified, only a few of them are extensively studied. For example, the number of papers on salidroside, verbascoside, echinacoside, forsythoside and isoverbascoside are 1746, 1258, 538, 370 and 230, respectively. And the numbers of citations of the papers about verbascoside, salidroside, echinacoside, forsythoside and isoverbascoside are 19356, 14352, 6468, 3234 and 4098, respectively. Other PhGs have fewer than 100 papers published. The number of papers published and number of citation of the papers of specific PhGs are also shown in Figure 3.

Despite the many promising biological activities, PhGs have failed to fulfill the therapeutic applications due to poor bioavailability[3]. The bioavailability of verbascoside was found to be 0.12% in rats after verbascoside was given at the dosages of 100 mg/kg oral administration (p.o.) and 3 mg/kg intravenous injection (i.v.)[70], but the bioavailability of verbascoside in dogs was around 4% after verbascoside was given at 40 mg/kg intragastric administration (i.g.) and 5 mg/kg i.v.[71]. The bioavailability of echinacoside, and angoroside C in rats at the dose of 100 mg/kg i.g. and 5 mg/kg i.v., was reported to be 0.83%[72] and 2.1%[73], respectively. The bioavailability of forsythiaside (100 mg/kg p.o. and 5 mg/kg i.v.) and poliumoside (200 mg/kg p.o. and 10 mg/kg i.v.) in rats was 0.5%[74] and 0.69%[75], respectively. Feng et al. compared the pharmacokinetic and bioavailability characteristics of savaside A, verbascoside, and isoverbascoside in rats after the compounds were given at the dosages of 1000 mg/kg p.o. and 5 mg/kg i.v.. The bioavailability order of the three PhGs appears to be verbascoside > isoverbascoside > savaside A[76]. Zhang et al.

investigated the pharmacokinetic of four PhGs (verbascoside, isoverbascoside, martynoside, and crenatoside) after orally administrated 10.0 g crude *Acanthus ilicifolius* herb /kg to rats. Although the four PhGs share similar molecular structures, they displayed different elimination half-lives ($T_{1/2}$), and different areas under the curves (AUC_{0-t}), ranging from 3.4 to 9.0 h, and 1826.3 to 23.6 μg/L×h, respectively[77]. Different dosages and administrative patterns might affect the bioavailability of PhGs. However, there is one exception. The bioavailability of salidroside was reported to be 51.97%[78]. As for the reasons why the bioavailability of salidroside was significantly higher than other PhGs, this may be ascribed to its relatively simple structure (Figure. 2). Salidroside belongs to monosaccharidic PhGs consisting of phenylethanol and sucrose, and the relatively large polarity allowed it to be easily excreted from the urine without complicated metabolic processes. The higher absorption of salidroside may also lead to its obviously higher bioavailability than other PhGs (section 5.1). Numerous approaches such as bioenhancers, β-cyclodextrin encapsulation, liposomal PhGs, nanoparticles and phospholipid complex have been applied to improve the bioavailability of PhGs.

There have been a number of reviews on PhGs since the 90's. As early as 1994, Jiménez and Riguera reviewed the isolation, purification, as well as structure and biological activity of PhGs[2]. Pan et al. highlighted the pharmacological activities of natural PhGs in 2003[79]. Fu et al. summarized the phytochemistry and bioactivity of PhGs in 2008[10]. Radev et al. published a mini review on pharmacological effects of PhGs in 2010[80]. Xue and Yang summarized advances in the phytochemistry, pharmacology and pharmacokinetics of PhGs in 2016[3]. Alipieva et al. reviewed the biosynthesis and pharmacological significance of verbascoside, the most popular phenylethanoid glycoside in 2014[9]. Liu et al. generalized the distribution, extraction methods, poor pharmacokinetics and therapeutic uses of echinacoside in 2018[81]. Tao et al. gave a detailed summary of chemical, pharmacological, toxicological, and clinical studies of various *Rhodiola* species with salidroside as the characteristic chemical constituents in 2019[82]. However, there are no comprehensive reviews concerning the stability, biotransformation, clinical application and bioavailability of PhGs. This review will summarize the latest information on the chemistry, pharmacology, stability, clinical application, pharmacokinetics, metabolites and biotransformation of PhGs. Recent advances in methods such as bioenhancers and nanotechnology to improve the bioavailability of PhGs will also be summarized. The existing scientific gaps of PhGs in knowledge are also discussed, highlighting research directions in the future.

2. Pharmacology of PhGs

PhGs have been reported to have various bioactivities in cell and animal models. Herein, the potential health benefits of PhGs are summarized (Figure 4), and the structure-activity relationship and mechanisms of PhGs' pharmacology are highlighted.

2.1 Antioxidant and free radical scavenging activity

Many PhGs and extracts rich in PhGs have shown powerful antioxidant activity. Two new PhGs named macrophylloside E and macrophylloside F, together with eight known PhGs (jionoside C, forsythoside B, alyssonoside, verbascoside, isoverbascoside, martinoside, isomartinoside and leucosceptoside) were isolated from *Callicarpa macrophylla*. All the ten PhGs showed high to moderate antioxidant effect with the IC_{50} from 2.72 to 38.65 μM in the DPPH assay[43]. Verbascoside isolated from *Plantago major* can significantly scavenge both DPPH (IC_{50}, 11.27 μM) and superoxide radicals (IC_{50}, 1.51 μM). Verbascoside can also inhibit lipopolysaccharide induced production of nitric oxide in RAW264.7 macrophages (IC_{50}, 75.0 μM) [83]. Seven PhGs (plantalide A, verbascoside, plantamajoside, martynoside, himaloside B, desrhamnosyl isoverbascoside and plantainoside D) discovered from *P. asiatica* showed DPPH radical scavenging activity with the IC_{50} values ranging from 22.9–88.5 μM. While other 22 compounds from *P. asiatica* showed weak antioxidant activity[85]. In addition, verbascoside and salidroside were demonstrated to be two major PhGs contributing to the great antioxidant capacities of *Osmanthus fragrans* flowers[85]. All nine PhGs (magnolosides Ia, Ib, Ic, IIa, IIb, IIIa, Iva, and Va and crassifolioside) from *M. officinalis* were found to possess strong free radical scavenging potential with the IC_{50} ranging from 11.79 to 20.99 μM, and magnoloside I_a (IC_{50}, 11.79 μM) was the strongest one[86]. The DPPH radical scavenging capacity of crassifolioside (IC_{50}, 21.38 μM), magnoloside IIa (22.94 μM), and magnoloside IIb (24.62 μM) was weaker than that of magnoloside Ia (11.79 μM), magnoloside Ic (12.99 μM), magnoloside Ib (16.23 μM), and magnoloside Va (20.99 μM). As we can see from the structures of these compounds, crassifolioside, magnoloside IIa and magnoloside IIb contained three sugars while magnoloside Ia, magnoloside Ic, magnoloside Ib, and magnoloside Va contained two sugars. More sugars mean larger steric hindrance in compounds and prevent them from easily approaching the free radicals, finally causing the weaker DPPH radical scavenging capacity. In addition, compared with the other seven PhGs, magnoloside IIIa (32.18 μM) and magnoloside IV (35.17 μM) with two adjacent phenolic groups only in one side exhibited poor activity[86]. Furthermore, benzene ring plane conjugation in PhGs can be increased by the α, β-conjugated unsaturated ester structures and allow electron delocalization to inhibit free radicals[86].

2.2 Neuroprotective effect

Verbascoside, isoverbascoside, salidroside, and echinacoside exhibited antioxidant and neuroprotective activities in hydrogen peroxide induced apoptosis in PC12 cells via the nuclear factor erythroid 2-related pathway[87]. CaleolariosideB, paraboside B, and paraboside II isolated from *Paraboea martinii* effectively protected PC12 cells from H_2O_2-induced damage by upregulating HO-1[88]. It is believed that β amyloid peptide (Aβ) is a major cause of Alzheimer's disease[89]. Total PhGs extracted from *C. Herba* at concentrations of 5, 25 and 50 μg/mLincreased the viability and decreased LDH and MDA release by PC12 cells injured with $A\beta_{1\text{-}42}$[90]. Torenoside B and savatiside A were demonstrated to improve the enzyme activity of GSH-Px and SOD, decrease the content of MDA and ROS, and downregulate intracellular Ca^{2+} concentrations and Calnexin expression in $A\beta_{25–35}$ induced SH-SY5Y cells[91]. Verbascoside, salidroside, and PhGs from *C. Herba* have significant protective potential against oxidative stress induced by Aβ[92, 93]. The characteristic pathology in Parkinson's disease is the degeneration of dopamine neurons in the substantia nigra pars compacta[94]. Campneoide and tubuloside B can protect neurons from 1-methyl-4-phenylpyridinium induced apoptosis *in vivo* [95, 96]. Verbascoside has potential therapeutic value against PD through attenuating the oxidative stress and activating the Nrf2/ARE signaling pathway[97]. SAMP8 mice, a model for AD, were administered by PhGs extracted from *C. Herba* daily intraperitoneally at 25, 50, or 100 mg/kg/day for 30 days. PhGs were found to improve cognitive deficits in SAMP8 mice by improving synaptogenesis and synaptic plasticity[98]. It has been reported that the mean lifespan of *caenorhabditis elegans* was extended by 13.64% and 15.82% after treated with 200 μM and 300 μM ECH, respectively. The protective effect of ECH on Aβ-induced toxicity in *C. elegans* was almost equal to that of ginkgolide A, a well-known agent with positive effects for AD[99].

Liu et al. synthesized eight PhGs derivatives based on calceolarioside A, and studied their neuroprotective effects in PC12 cells. The results showed that seven compounds could protect the cell damage or death from the free radical damage except the chloro-substituted analog. The structure-activity relationship indicated that the catechol moiety might not monopolize the bioactivity but probably could play an important role in neuroprotection and the glucose moiety seemed not important for the neuroprotection[100]. The findings were consistent with the recent structure-activity of caffeic acid phenethyl ester analogs[101, 102].

2.3 Hepatoprotective effect

Verbascoside, isoverbascoside, echinacoside, tubuloside B, cistanoside A and 2-acetylacteosid offer hepatoprotective effects via multiple mechanisms including strengthening antioxidant defense system, free

radicals scavenging, and blocking cytochrome P450 biotransformation[103]. Leucoseceptoside A, crenatoside, martynoside, and 3-*O*-methylcrenatoside extracted from *Incarvillea compacta* alleviated CCl_4-induced hepatotoxicity by enhancing the activity of superoxide dismutase, decreasing the intracellular ROS and malondialdehyde content as well as activating NF-κB pathway[104]. Fourteen PhGs isolated from *Forsythia suspensa* were evaluated for their hepatoprotective effects on HepG2 cells damage induced by APAP. It was found that forsythoside N, forsythoside O, forsythenside A and forsythenside B exerted significant hepatoprotective activities[28] with the cell survival rates from 52.48% to 67.15%, 67.61%, and 64.88% at the concentration of 10 μM, respectively. Cistanoside A (125, 250, and 500 mg/kg/day) could alleviate ethanol-induced hepatotoxicity in mice by improving the activities of the activities of energy metabolism enzymes (Ca^{2+}-Mg^{2+}-ATPase, ATPase, and Na^{+}-K^{+}-ATPase), mitochondrial antioxidant enzymes (SOD, GST and CAT), and antioxidant defense system[105]. Besides, cistanoside A (100, 75, 50, and 25 μg/mL) suppressed the apoptosis of hepatocytes by increasing the expression of Bcl-2 and supressing c-fos[105]. Echinacoside (60 mg/kg, i.p.) could significantly protect LPS and D-galactosamine induced acute liver injury in mice due to its anti-apoptotic and anti-inflammatory activities[106]. PhGs from *C. deserticola* was assessed for their hepatoprotective activity *in vitro* and *in vivo*. Concentrations of 0.33, 1.00, 3.00 mg/mL PhGs could improve the HepG2 cells viability to almost 10%, 22% and 35%, respectively. After orally administered with PhGs at 200, 600 or 1800 mg/kg for 31 consecutive days, ICR mice with liver injury induced by alcohol showed improved hepatic indicators (superoxide dismutase, glutathione S-transferase, glutathione, glutathione peroxidase, malondialdehyde and triglyceride) levels[107].

Structure–activity relationship indicated that the catechol moiety on PhGs was important for the hepatoprotective activity[108]. Verbascoside (IC_{50}, 4.6 μM), 2′-acetylverbascoside (4.8 μM), isoverbascoside (5.3 μM), tubuloside A (8.6 μM) and echinacoside (10.2 μM) inhibited D-GalN-induced death of hepatocytes[109]. Verbascoside (IC_{50}, 4.6 μM) showed significantly stronger activity than kankanose (>100 μM), and echinacoside (10.2 μM) showed significantly stronger activity than cistanoside F (>100 μM), which indicated that aglycone was an important group for the activity[109]. As the activity of isoverbascoside (5.3 μM) was higher than kankanoside G (14.8 μM), it can be concluded that aglycone with the 4-hydroxy group showed weaker activity than that having 3,4-dihydroxy group[109]. The 8-O-β-D-glucopyranosyl part with 6′-O-caffeol group (Tubuloside B, 14.6 μM) showed weaker activity than that with 4′-O-caffeoyl group (2′-acetylverbascoside, 4.8 μM)[109]. The introduction of 6-*O*-β-D-glucopyranosyl (echinacoside < verbascoside) and 2′-O-acetyl moiety (2′-acetylverbascoside<verbascoside) could reduce the protective effect[109].

2.4 Anticancer activity

In a recent study, echinacoside was reported to possess antiproliferative activities (20 μg/mL, 9.57 %; 50 μg/mL, 26.67%; 100 μg/mL, 37.20%) on HepG2 cells by inactivating AKT pathway and decreasing TREM2 expression[110]. Verbascoside, echinacoside, cistantubuloside A, cistanoside A, and 2′-acetylverbascoside inhibited the proliferation of mouse skin melanoma cancer cell line KML with the inhibition rate ranging from 33% to 93%[111]. Pretreatment with 5, 10, 20, 40 and 50 μM salidroside for 48 h can inhibit the proliferation of human breast cancer MCF-7 cells to almost 70%, 60%, 55%, 45% and 30%, respectively. The mechanism maybe related with increasing caspase activity, down-regulating the Bcl-2 expression, and up-regulating the Bax expression. Moreover, salidroside treatment inhibited tumor growth in a xenograft tumor model. Compared with control group, after treated with salidroside (50 mg/kg body weight) on alternate days for 3 weeks, the weight and volume of tumor was decreased by 0.7 g and 300 mm^3, respectively[112]. Salidroside was reported to possess antitumor activity against Wilms' tumor[113], breast cancer[114], ovarian cancer[115], gastric cancer[116], skin cancer[117], renal cell carcinoma[118] and colorectal cancer[119]. Li et al. investigated the effects of PhGs extract from *C. tubulosa* (CTPG) on the inhibition of melanoma cell (B16-F10) growth. *In vitro*, 100 μg/mL of CTPG for 48 h or 200 μg/mL of CTPG for 72 h treatment inhibited the growth rates of B16-F10 cell to higher than 60% and 90%, respectively. CTPG can up-regulate the expressions of BAX, down-regulate the expressions of BCL-2, increase the generation of ROS, and reduce the mitochondrial membrane potential *in vitro*. Furthermore, subcutaneously administering 400 mg/kg CTPG in mice every 2 days for up to 15 days lasted the survival of mice from 8.3% to 41.7% [120]. Verbascoside from *Pedicularis striata* could inhibit cancer cell growth and cell cycle in G2/M phase, induce apoptosis and inhibition of telomerase activity and reduced telomere length[121]. It should be noted that not all PhGs exhibit anticancer properties. For example, Kirmizibekmez et al. tested the cytotoxic activity of four PhGs (plantainoside D, calceolarioside D, neocalceolarioside D and lugrandoside) against a series cancer cell lines, namely SH-SY5Y, T98G, A375, HT29, MCF-7, PC3. All the four compounds showed no toxicity against the six cancer cell lines at the concentration of 1–50 μM[122]. A number of structure-activity relationships proved that the caffeic acid moiety and catechol group are essential for the cytotoxicity of PhGs. The number of acetyl moieties and their position in the aliphatic rings also play an important role in the anti-proliferative activities of PhGs[123-125]. The antiproliferative activity of verbascoside was almost twice as that of echinacoside and calceolarioside. The similar cytotoxic activity of calceorioside A and verbascoside suggest that rhamnose substitution does not influence the cytotoxic

activity of PhGs[126]. Verbascoside inhibited about 23%–30% of the proliferation activity of the cancer cells, which is almost twice as many as echinacoside (10%–18%), calceolarioside A (13%–18%), and calceolarioside B (5%–15%). The higher antiproliferative activity may be related to the α-Rha-(1→3)-Glc disaccharide unit and the 4-caffeoyl function in verbascoside[127]. The structure-cytotoxicity relationships among 14 PhGs compounds indicated that the fewer sugar units they have, the stronger activities they may have. Furthermore, the position of phenolic acid does not affect the activity. Besides, methylation of the phenolic hydroxyl groups has an adverse impact on the activity[128].

2.5 Anti-inflammatory activity

The anti-inflammatory activity of PhGs is often connected to suppression of MAPK, NF-κB, and JAK-STATs pathways and activation of Nrf2 pathway[129]. Wu et al. confirmed that PhGs (verbascoside, parvifloroside A, syringalide A, 3′-α-L-rhanmnopyranoside, forsythoside B, poliumoside and alyssonoside) from *C. kwangtungensis* provided protection against LPS-induced inflammatory response in RAW 264.7 macrophages by activating Keap1/Nrf2/HO-1 signaling pathway[130]. Echinacoside attenuated LPS-induced inflammation in rat intestine epithelial cells by suppressing the mTOR/STAT3 pathway[131]. Verbascoside can inhibit the release of β-hexosaminidase, arachidonic acid and histamine in RBL-2H3 cells through inhibiting MAPK and JNK pathways and Ca^{2+} independent phospholipase[132-134]. Verbascoside (30, or 60 mg/kg) was shown to decrease inflammatory response against LPS-induced acute lung injury in mice by inhibiting NF-κB signaling pathway[135]. Gao et al. investigated the anti-inflammatory effects of verbascoside, isoverbascoside, torenoside B and savaside A and found that isoverbascoside (80 μM), possessed the strongest activity on inhibiting the expression of iNOS and COX-2[136]. Isoverbascoside exerts anti-inflammatory via modifying NF-κB and MAPK pathways[136]. Forsythiaside A was reported to have protective potential on LPS-induced inflammation in BV2 microglia cells and primary microglia cells via increasing Nrf2 and HO-1 levels and suppressing NF-κB pathway[137]. Forsythiaside A could attenuate inflammation in acute liver injury animals by activating Nrf2 and inhibiting NF-κB pathway[138]. PhGs from *Phlomis younghusbandii* exerted anti-inflammatory properties on acute hypobaric hypoxia-stimulated HACE in rats by rehabilitating the oxidative stress levels and inhibiting the expression of pro-inflammatory cytokines regulated by the NF-κB signaling pathways[139].

The anti-inflammatory activity of seven PhGs on inhibiting NO production showed that leucosceptoside A (IC_{50}, 9.0 μM), lipedoside A-I (11.6 μM), verbascoside (12.8 μM), isoverbascoside (13.7 μM), and campneoside II (22.1 μM) possessed stronger activity than martynoside (>100.0 μM) and angoroside C

(>100.0 μM). This indicated that the two adjacent hydroxide groups in PhGs may be related to their anti-inflammatory activity[140]. Yang et al. demonstrated that PhGs with two sugar groups possessed weaker activities than others[141].

2.6 Antiviral, antibacterial and antiprotozoal activity

Lippiarubelloside A and lippiarubelloside B, together with four known PhGs, verbascoside, isoverbascoside, forsythoside A, and poliumoside, isolated from *Lippia rubella* could inhibit the growth of *Cryptococcus neoformans* at the concentrations of 15-125 μg/mL[32]. Total PhGs extract from *Monochasma savatieri* showed significant antibacterial effects at a concentration from 0.0625 to 16 mg/mL[142]. Verbascoside and forsythoside B showed high antibacterial activities against five strains of *Staphylococcus aureus* from 64 g/L to 256 g/L, which were comparable to that of norfloxacin[143]. When used alone at the dose of 200 μg/mL, verbascoside had no inhibitory activity against clinical isolate of *Escherichia. coli* and *Staphylococcus. aureus*. However, co-administration of verbascoside and gentamicin showed a synergistic effect against *E. coli* and *S. aureus*. This indicated that verbascoside could be applied to overcome bacterial resistance caused by traditional medicines[144]. Isoforsythiaside and forsythiaside are the main antibacterial constituents in *Forsythia suspense*, which is often applied to treat the infection in upper respiratory tract. Isoforsythiaside and forsythiaside well inhibited the growth of *E. coli, P. aeruginosa* and *S. aureus*[145, 146]. In addition, forsythoside H exhibited strong inhibitory effects against *B. vulgare, B. dysenteriae, M. pneumonia,* and *A. bacillus*[147]. Verbascoside has antiviral activity *in vitro* and anti-influenza activity *in vivo*. And the antiviral mechanism of verbascoside was related to the activation of ERK and enhancement of IFN-γ production[148]. Forsythiaside and calceolarioside B showed significant antiviral potential on respiratory syncytial virus *in vitro*[149]. Forsythiaside inhibited the infectivity of avian infectious bronchitis virus[150]. Taraffinisoside A, a new PhGs isolated from *Tarphochlamys affinis,* showed antihepatitis B activity with IC_{50} values of 0.50 and 0.93 mM against hepatitis B surface antigen and hepatitis B eantigen, respectively[67]. Forsythoside A from *F. suspensa* decreased the viral titers of different influenza virus subtypes in cell cultures at the dose of 160 μM. Forsythoside A also increased the survival rate of the mice in an influenza virus infection model at 5 or 10 μg/g body weight [151]. Hu et al. evaluated the anti-influenza virus effects of PhGs *in vitro* and *in vivo*. PhGs at 0.5 mg/mL could inhibit the influenza A virus H1N1 type infection of Madin Darby canine kidney cell *in vitro*. PhGs at 300 and 900 mg/kg significantly reduced the mouse lung index ($p<0.05$), alleviated influenza-induced lethality and clinical symptoms, and prolonged mouse survival time ($p<0.05$). The mechanism maybe related to up-regulating IFN-γ[152].

It has been reported that verbascoside possessed antiprotozoal activity against *Trypanosoma brucei rhodesiense, Leishmania infantum*, *L. donovani*, and *L. amazonensis*[153, 154]. Verbascoside showed an EC_{50} of 19 μM against *L. promastigotes* and is a competitive arginase inhibitor with Ki of 0.7 μM[155]. Among seven PhGs extracted from *Tecoma mollis*, luteoside B and luteoside A showed the strongest antileishmanial activity with the IC_{50} values of 6.7 and 15.1 μg/mL, respectively[156].

Little information is available about the structure-activity relationship of PhGs in its antiviral and antibacterial activities. Kyriakpoulou et al. discovered that samioside is more active than verbascoside against four strains of bacteria, indicating that an additional sugar moiety (apiose) at C-4 of rhamnose could contribute to the antibacterial activity[157]. Although phlinoside C and forsythoside B have a similar structure, phlinoside C hardly inhibit multi-drug-resistant strains of *S. aureus.* This indicated that introducing the third glycoside (rhamnose) to forsythoside B might cause its inactivity[143].

2.7 Antidiabetic activity

A new PhGs named flavaioside from *Scrophularia flava* showed α-glucosidase inhibitory activities with IC_{50} value of 6.50 μg/mL. In addition, flavaioside possessed a significant inhibitory activity on the α-glucosidase enzyme, and the inhibitory activity (91.85%) was comparable with the known anti-type 2 diabetic drug, acarbose (92.87%)[158]. The *in vitro* experiments showed that verbascoside, echinacoside, isoverbascoside, 2'-acetylverbascoside, tubulosides A, tubulosides B, syringalide A' 3-*O*-rhamnose, campneoside I, and kankanoside J_1 from *C. tubulosa* could offer strong inhibition against lens aldose reductase with their IC_{50} of 3.1, 1.2, 4.6, 0.071, 8.8, 4.0, 11.1, 0.53, and 9.3 μM, respectively. Especially, 2'-acetylverbascoside showed the similar activity with epalrestat, a clinical aldose reductase inhibitor[159]. Verbascoside and echinacoside were demonstrated to improve glucose tolerance and decrease glucose level in mice at doses of 250-500 mg/kg[159]. Verbascoside and echinacoside could suppress the increased postprandial blood glucose level by inhibiting glucose transporter 1-mediated glucose uptake[160]. Isocampneoside II isolated from *P. coreana* could significantly inhibit recombinant human aldose reductase with the IC_{50} of 9.72 μM. Furthermore, verbascoside, isoverbascoside, isocampneoside II and cistanoside F effectively inhibited sorbitol accumulation in a rat lens incubated with a high concentration of glucose by almost 70.6, 47.9, 71.3, and 31.7% at 50 μM, respectively[161]. Compared with control group, three weeks oral administration of verbascoside (10, 20, and 40 mg/kg) caused a significant reduction of blood glucose to 111.30, 74.88, and 75.15 mg/dL, respectively, in diabetic rats. Regarding serum insulin levels, oral treatment with verbascoside (10, 20, and 40 mg/kg) elevated the serum insulin level to be 3.23, 5.38, and

6.80 μIU/mL, respectively, in diabetic rats[162].

2.8 Other activities

Wu et al. investigated the anti-obesity properties of PhGs form *Ligustrum purpurascens*. The results showed that PhGs inhibited α-chymotrypsin, trypsin and pepsin with the IC_{50} values of 0.42, 0.38, and 0.68 mg/mL, respectively. Verbascoside exerted the anti-obesity effects by inhibiting pancreatic lipase. Verbascoside bounded to lipase at Ka = 1.88×10^4/l mol[163]. The anti-obesity effect of PhGs from *L. purpurascens* against fatty diet-fed mice was associated with the up-regulating of mRNA and protein levels of adipose leptin[164]. Echinacoside (0.01-10 nmol/L) was reported to boost bone regeneration in MC3T3-E1 cells by enhancing receptor activator of NF-κB ligand (RANKL)[165]. Similarly, 12 weeks' daily i.g. administration of echinacoside (30, 90, and 270 mg/kg/day) to ovariectomized (OVX) rats significantly increased osteoprotegerin (OPG) level and decreased RANKL level[166]. Compared to OVX group, 270 mg/kg/day echinacoside treatment caused the highest levels of OPG and OPG/RANKL ratios (150.14% and 197.64%)[166]. After 12 weeks' daily orally administration of echinacoside (30, 90, 270 mg/kg/day) in OVX rats, the urine concentration of calcium, inorganic phosphorus, and hydroxyproline was increased by 92.23%, 66.67% and 36.41%, respectively, in 270 mg/kg/day group[167]. Cistanoside A (p.o., 20, 40 and 80 mg/kg/day for 12 weeks) was found to promote bone formation and prevent bone resorption in OVX rats by downregulating TRAF6, coordinating the inhibition of NF-kB pathway and stimulating PI3K/Akt pathway[168].

3. Clinical applications of PhGs

Although PhGs exhibit many bioactivities in cell or animal models, the poor bioavailability of PhGs restricts their clinical applications. Various PhGs-based products including Traditional Chinese Medicines (oral liquid, capsules and tablets), dietary supplements and tea are summarized in Figure 5.

In a randomized, single-center and double-blind clinical trial (phase II) conducted in 100 patients having cardiovascular risk factors, orally administration of verbascoside tablet (50 mg/tablet, twice daily) for 2 weeks can significantly decrease platelet aggregation (PA) from 51% to 39% [169]. According to the ongoing and unpublished clinical trials about PhGs on the International Clinical Trials Registry Platform (http://apps.who.int/trialsearch), a comparative evaluation of verbascoside and silymarin as hepatoprotective agents in acute hepatitis patients had been performed (Main ID: CTRI/2008/091/000247), but the results were not provided in the platform. Qiu et al. assessed the efficacy of verbascosides from

Rehmannia. glutinosa combined with irbesartan in treating chronic primary glomerulonephritis in 479 patients. The patients were randomly divided into treatment group (*R. glutinosa* verbascoside, 200 mg/capsule, two capsules one time, twice daily; and irbesartan, 150 mg/tablet, one capsules one time, once daily) and the control group (irbesartan, 150 mg/tablet, one capsule one time, once daily). After 8 weeks treatment, the mean reduction of proteinuria in 24h in treatment group (36.42%) was significantly higher than that in control group (27.97%), indicating the combination of *R. glutinosa* verbascosides and irbesartan can reduce proteinuria more effectively than irbesartan alone[170]. From the website of Clinicaltrials.gov., a phase II clinical study (Identifier: NCT02662283) had been conducted to test the therapy effect of Reh-verbascoside (general verbascoside from rehmanniae leaves) in patients with immune globulin a nephropathy. But it is a pity that the results of this clinical trial are not available from the website. Salidroside powder (600 mg/day) was shown to prevent the symptom of early left ventricular regional systolic dysfunction caused by epirubicin in 60 patients with breast cancer[171].

In China, *C. tubulosa* glycosides (CTG, Memoregain®) have been approved as a treatment for vascular dementia and produced by Sinphar Tianli Pharmaceutical Company (Hangzhou, China) (Figure 5). This is the first Chinese government approved drug containing PhGs. An open-label, no placebo-controlled clinical trial was conducted to study the effect of CTG capsules for treating AD. A total of 18 patients with AD were administered by 300 mg CTG capsules, 3 times per day for 48 weeks. The Mini-Mental State Examination score, Alzheimer's Disease Assessment Scale–cognitive subscale score, Activities of Daily Living score, Blessed Behavioral Scale, and Clinical Global Impression scales all showed no significant difference from baseline, indicating that AD patients did not show significant aggravation of cognitive function after 48 weeks[172]. Observations from 131 patients with vascular dementia showed that CTG (0.3 g/capsule, 6 capsules per day, 3 months) was more effective than positive control (hydergine, 1 mg/ tablet, 6 tablets per day, 3 months) against vascular dementia[173]. Peng et al. and Yuan et al. also reported that CTG (0.3 g/capsule, 6 capsules per day, 48 weeks) can improve cognitive function in the early dementia and mild dementia patients[174, 175]. From the website of http://apps.who.int/trialsearch, a clinical trial about CTG for treatment of amyotrophic lateral sclerosis has been carried out (Main ID: ChiCTRIOR-15006524). Hopefully, the results of this clinical trial will be published soon. Echinacoside is one of the active ingredients in *C. Herba* and the main active component of Memoregain(®). In addition, two new agents named Echinacoside and Naoqing Zhiming tablet derived from echinacoside have been approved for clinical trials by the Chinese government in 2107. It should be noted that the clinical trials of Echinacoside and Naoqing Zhiming tablet were applied by Huayi Shennong Pharmaceutical Company (Beijing, China)

set up by Prof. Tu Pengfei from School of Pharmaceutical Sciences, Peking University. Prof. Tu has made great contribution to the development of Cistanche deserticola industry, and Memoregain(®) was also developed based on the researches of Prof. Tu. It has been demonstrated that cistanches herba capsule (0.3 g/capsule, 3 capsules per day, 48 weeks) could increase cognitive abilities in AD patient's and slow down their hippocampus atrophy process. It also decreased the expressions of TNF-α, T-tau, and IL-1β in cerebrospinal fluid of AD patients as the similar effect as Donepezil tablet (5mg/tablet, 1 tablet per day, 48 weeks)[176].

Herbs used together, rather than a single herb or a single compound, are the commonly used forms in traditional Chinese medicines (TCM), and often have significant clinical effects. PhGs are the active and characteristic compounds of *F. forsythiae*[177]. And *F. forsythiae* has been extensively used in TCM preparations, such as Shuang Huang Lian oral liquid, Niu Huang Shang Qing tablets and Yin Qiao Jie Du tablets, etc., which have long been used to treat respiratory tract infection[178] (Figure 5). In the 2015 edition of Chinese Pharmacopoeia, over one hundred TCM preparations containing *F. Forsythiae* are listed (Pharmacopoeia Commission of PRC, 2015). Another example is that Bu Shen Huo Xue Granule with *C. Herba* as a main active component, can significantly improve the clinical symptom of patients with PD[179].

4. Stability of PhGs

As we can see from the chemical structure of PhGs, there are several phenolic hydroxyl groups, ester bonds and glycosidic bonds, which makes them be easily oxidized and degraded. In addition, the intra-molecular acyl migration, and cis-/trans configurational conformation of acyl and glycosyl widely occur in this chemical cluster. These structural properties make PhGs labile compounds. PhGs are vulnerable to be degraded by various factors such as light, temperature and pH in theory.

PhGs were found to be unstable under light exposure, high temperature, and high pH conditions[180]. The content of total PhGs (TPG) of *O. fragrans* flowers in water for 90 days was significantly decreased by 87% at 50 °C. And TPG was degraded by 84.25% after 7 days at 80 °C. Increasing of pH (from 5.0 to 9.0) accelerated the degradation of PhGs. At the same temperature (20 °C), the degradation rate of TPG in light was significantly higher than dark, indicating PhGs were unstable in light. The degradation patterns of salidroside and verbascoside were the same of TPG[180]. Verbascoside was more stable in a weak acid medium, low temperature and dark conditions. Under the condition of pH 7, verbascoside was completely degraded after two weeks (room temperature) and three weeks (40 ºC). While the degradation rate of verbascoside was 27% over 60 days, in the dark and room temperature at the pH of 5[181]. Oyourou et al.

assessed the stability of verbascoside in crude plant extract during storage. After 2 and 4 h exposure to sunlight, only 43.2% and 18.6% of the verbascoside were remained in the extract[182].

In order to imitate the storage condition of verbascoside at room temperature for two years, verbascoside was put in an oven at 56 ºC for 2 weeks. Verbascoside in crude plant extract was found to significantly decompose, with only 13.7% left after 2 weeks' exposure. It indicated that verbascoside is unstable after stored for a long period[182]. Verbascoside in bitter tea was isomerized to isoverbascoside when heated in the boiling water[183], while verbascoside remains intact during the process of steam pasteurization at 99 ºC for 150 s[184]. This phenomenon was inconsistent with the findings that 98.2% and 5.4% of verbascoside was left following steam distillation and hydrodistillation, respectively[182]. It has been reported that 62.4% and 100% of verbascoside were left at pH 7 and 3, respectively, after 24 h[185]. The reduction level of verbascoside at pH 7 was in agreement with the results of Vertuani et al.[181]. Verbascoside was moderately stable during digestive conditions *in vitro* with a recovery rate of 53%, while isoverbascoside was less stable with a recovery rate of 13%[186]. When echinacoside was stored in methanol, two primary products verbascoside and cistanoside A, could be observed by HPLC chromatogram． And *cis*-echinacoside，*cis*-verbascoside，and *cis*-cistanoside A were detected after careful analysis of the 1H-NMR spectra of echinacoside, verbascoside and cistanoside A. These findings indicated that methylation and hydrolysis are the main transformation pathways of echinacoside in methanol, and mild transformation could also occur by cis/trans-configuration transferring in the caffeoyl group[187]. PhGs were reported to be stable in tincture with 80% left after 6 months, probably because of the weak acid medium in tincture[188].

5. Pharmacokinetics of PhGs

The main pharmacokinetic parameters of several PhGs in plasma are summarized in Table 3[70-76, 78, 189-194].

5.1 Absorption

The absorption of salidroside, verbascoside, isoverbascoside and echinacoside in Caco-2 cells were poor, and their transportation was mainly via passive diffusion (less than 3.0%)[195, 196]. Verbascoside was poorly absorbed with low apparent permeability (Papp) (4.75×10^{-7} cm/s). The peak accumulation of verbascoside and isoverbascoside was at 30 min *in vitro,* indicating their rapid uptake. But the uptake efficiency was very low (0.1-0.2%) [196]. The intestinal absorption of verbascoside in viable and healthy human colonic tissues demonstrated that verbascoside was absorbed rapidly, but the total accumulation efficiency was less than 0.12%. Major absorption of verbascoside happened in proximal tract of colon (5 to 15 min), and then it was descending to colon (30 to 60 min) and sigmoid rectum colon after 60 min[197]. A bioavailability study of

oral versus intravenous verbascoside dosing in rats reported that verbascoside given at the dose thirty times higher than the intravenous dose, lead to the C_{max} of 0.13 and 48.6 μg/mL and the $T_{1/2}$ of 92.1 and 10.7 min for oral and intravenous routes, respectively[30]. Similarly, verbascoside was reported to be absorbed extremely fast in rats. However, the maximum serum concentration was very low (C_{max}, 312.54 ng/mL) [189]. The uptake of verbascoside and plantamajoside was very quick with T_{max} values of 13.3 and 16.7 min, respectively. C_{max} values of verbascoside and plantamajoside in plasma were 135.5 and 172.3 ng/mL, respectively[198].

Echinacoside permeated poorly with the Papp of zero after 90 min *in vitro*. The uptake of echinacoside was at the same level of mannitol which is a known poor intestinal absorption compound[199]. Echinacoside can pass the intestinal barrier through carrier-mediated transport. The Peff values of jejunum, duodenum, and ileum was at the same level (0.006 μg/s), higher than that of colon (0.002 μg/s), suggesting that intestinal absorption of echinacoside was site dependent[200]. Echinacoside was absorbed quickly after i.g. administration at 100 mg/kg in rats, exhibiting the C_{max} of 312.54 ng/mL after 0.29 h. However, the maximum serum concentration was very low with the C_{max} of 612.2 ng/mL[32]. In humans, echinacoside cannot be detected in plasma after echinacea tablet ingestion[201].

The permeability of forsythiaside A in the basolateral-to-apical direction was similar to that in apical-to-basolateral direction in Caco-2 cell model[202]. A similar research indicated that the absorption of forsythiaside A was mainly involved with paracellular transport route, and P-glycoprotein, multidrug resistance related proteins and uptake transporters might participate in its uptake in the intestine[203]. In addition, no statistical difference of absorption was found for forsythiaside among gastric, duodenum, jejunum, ileum and colon, indicating no specific absorption site of forsythiaside[204]. When given i.g. administration of 100 mg/kg forsythiaside to rats, a maximum serum concentration of 122.2 ng/mL was observed at 20 min[73].

The rapid but low absorption was also found in poliumoside and angoroside C. After i.g. administration of poliumoside at 200 mg/kg in rats, the T_{max} and C_{max} were calculated to be 30 min and 561 ng/mL, respectively. Angoroside C can be absorbed extremely quickly (T_{max}=15 min) after oral administration and can be eliminated very rapidly ($T_{1/2}$, 1.26 h) [75].

Unlike the rapid but low absorption pattern of the PhGs summarized above, salidroside was reported to have a rapid and high absorption. After p.o. administration of 5 mg/kg salidroside in rats, salidroside showed rapid oral absorption with a T_{max} of 30 min. The C_{max} of salidroside was approximately 6493 ng/mL, which is almost twenty times higher than that of verbascoside and echinacoside[192]. Salidroside has a rapid and

high absorption with the C_{max} of 3716.73 ng/mL and 4300 ng/mL, after i.g. administration of 100 mg/kg and 12 mg/kg in rats, respectively[78, 193]. The high absorption of salidroside may lead to its obviously higher bioavailability than other PhGs.

5.2 Distribution

The distribution of PhGs in tissues is crucial for its bioactivity, although only few studies have reported on it. Wen et al. investigated the distribution of verbascoside in rats after p.o. administration (40 mg/kg) and found that verbascoside reached maximum level in most organs at 0.17 or 0.50 h post-administration. The highest concentration of verbascoside occurred in intestine (26474.50 ng/gtissue), followed by lung (23 466.07), stomach (19918.21) and muscle (9498.13). The levels of verbascoside in intestine, lung, stomach and muscle were significantly higher than that in other tissues like spleen, kidney, liver, heart, brain, adipose, ovary and testis[189]. After 0.17 h, verbascoside cannot be detected in ovary and testis. Verbascoside in adipose and in kidney was undetectable after 1.5 h. The levels of verbascoside in all tissues remarkably reduced after 1.5 h, suggesting verbascoside cannot cause accumulative damage effect *in vivo*. In addition, a little amount of verbascoside was detected in brain, indicating verbascoside can pass the blood-brain barrier[189]. The verbascoside concentration in different brain regions ranged from 0.45 to 0.68%. There was no statistical difference of verbascoside concentration in different brain regions (brain stem, cerebellum, hippocampus, striatum, cerebral cortex, and the rest of brain) after i.v. administration of 10 mg/kg verbascoside in rats[70]. After i.g. administration of 200 mg/kg verbascoside and 200 mg/kg echinacoside in rats, their relative content in plasma, feces, urine and bile was calculated. Only 1.54% of echinacoside and no verbascoside was detected in plasma[205]. Sibirioside A (200 mg/kg) and angoroside C (200 mg/kg) from *S. Radix* were widely distributed in heart, lung, liver, stomach, kidney, and small intestine in rats[206]. The highest content of sibirioside A was in stomach and small intestine, followed by the kidney and liver. But no angoroside C was detected in the viscera except for stomach and small intestine. The highest level of angoroside C was found in lung 15 min after p.o. administration and angoroside C is distributed rapidly and cannot be detected from all of the organs after 6 h[206].

Distribution study in rats after i.v. administration of 15 mg/kg salidroside showed that salidroside distributed rapidly into tissues after 15 min[207]. At all three time points (15, 40 and 120 min), the concentration of salidroside in plasma was higher than that in any tissues. Half of the unchanged salidroside was detected in urine over 48 h, but only 0.89 ‰ and 1.8 ‰ was detected in bile and feces, respectively[207]. Compared with i.g. administration, the distribution of salidroside in rats changed greatly under i.v.

administration. After i.v. administration of salidroside (50 mg/kg) to rats, the maximum levels of salidroside were mainly in liver, kidney and heart. However, salidroside was only found in liver after i.g. administration of salidroside (100 mg/kg)[208]. After 72 h, 64% and 23.8% of the administered salidroside was excreted in the urine, after i.v. administration and i.g. administration, respectively. After 72 h, 0.3% of the administrated amount was detected in feces after i.v. administration, while no salidroside was detected in faeces after i.g. administration[208].

5.3 Metabolites *in vivo*

Based on the metabolic pathways mentioned below, the metabolic pathways of PhGs *in vivo* are shown in Figure 6. 35 metabolites in rats orally administrated with verbascoside (100 mg/kg) were detected in rat urine. 19 metabolites belong to the parent compound and 16 metabolites belong to the degraded products of verbascoside. The metabolism processes include oxidation, glucuronidation, sulfation, and methyl conjugation, with methylation of the most easily occurred[209]. Verbascoside was easily hydrolyzed to degraded products, which is responsible for its low oral bioavailability[209]. After p.o. administration of verbascoside, 44 metabolites were identified in rats' plasma, urine, and feces samples. This is the first time to report the isomerization of verbascoside to isoverbascoside[210].

Eight metabolites of echinacoside, mainly methylation and glucuronidation conjugates, were found in the biliary of rats after oral dose of 200 mg/kg echinacoside [211]. A later study identified 13 metabolites of echinacoside in rat urine and feces samples after p.o. administration of 1500 mg/kg echinacoside[212]. In 2019, Song et al. reported that 19 metabolites were identified in blood, urine and feces samples of echinacoside (50 mg/kg, i.g.) treated rats by analyzing m/z values, retention time, and optimal collision energy. Echinacoside firstly underwent extensively hydrolysis to generate verbascoside, followed by intermediates such as caffeic acid and hydroxytyrosol. Afterwards, the two intermediates received sulfonation, glucuronidation, methylation, oxidation, reduction, and/or hydrogenation to finally generate M1−M16. In addition, acyl-migration and acetylization of verbascoside (M17) produced isoverbascoside (M18) and acetyl-verbascoside (M19)[213]. 3 metabolites of forsythiaside A (200 mg/kg, p.o.) were identified in rats, with 42 in urine, 22 in plasma and 15 in feces[214]. In general, forsythiaside A was mainly methylated, dimethylated, sulfated, glucuronidated, diglucuronidated, and cysteine conjugated. Hydroxyl group on caffeic acid of forsythiaside A was the major target metabolic site[214]. 66 metabolites of poliumoside (1000 mg/kg, p.o.) in rat feces samples were identified. The metabolic pathways of poliumoside involving in phase I were hydroxylation, hydration, hydrolysis, methoxylation, dehydrogenation and reduction; while

the phase II reactions were sulfation, dimethylation and acetylation. And hydroxylation was more likely to occur in the metabolic process. Verbascoside is a key degraded product of poliumoside[215]. After oral administration of poliumoside (1500 mg/kg), 34 poliumoside metabolites (30 from urine, 17 from plasma, and 4 from bile) were identified, which also demonstrated that verbascoside was a main degraded product of poliumoside and mainly existed in urine. The nine metabolic pathways of poliumoside were proposed as rearrangement, reduction, hydroxylation, hydration, dehydration, methylation, acetylation, hydrolyzation, and sulfation[216], which are partly in accordance with the result of Deng et al.[215]. Metabolites of salidroside in rats plasma samples indicated that salidroside was metabolized through glucuronidation, deglycosylation, sulfation, methylation, hydroxylation, and dehydroxylation *in vivo*[217]. After p.o. administration of *C. tubulosa* extract (400 mg/kg), the *in vivo* metabolites in urine and fecal were obviously different in healthy and chronic unpredictable stress model rats. The metabolic ability to generate secondary glycosides and aglycones in depressive rat intestinal microbiota was much weaker than that in normal rat intestinal microbiota. The reason may be related to structural changes of the intestinal microbiota induced by depression, which finally lead to decreased activity of related enzymes produced by intestinal microbiota[218]. The metabolites of angoroside C and sibirioside A were studied after orally administrating 200 mg/kg compounds to rats[206]. 25 metabolites of angoroside C were found mainly in urine via hydrolyzation, dehydroxylation hydrogenation, gluconylation, demethylation, and sulfation. And gluconylation was the prime and representative metabolic reaction[206]. As for sibirioside A, four metabolites were found, with one in urine, two in feces, and one in stomach. The less metabolites of sibirioside A maybe due to its simple molecular structure. The main metabolic reactions of sibirioside A were hydrogenation, sulfation, hydroxylation, dimerization methylation, and glycosylation[206].

6. Biotransformation of PhGs by microbiota *in vitro*

Intestinal bacteria are mainly involved in reduction, hydroxylation and hydrolyzation[219]. The metabolites of verbascoside in human or rat intestinal bacteria confirmed this point. Verbascoside was biotransformed to 14 metabolites through a series of reactions including isomerization, hydroxylation, hydrogenation, and dihydroxylation. The main metabolites of verbascoside was caffeic acid, hydroxytyrosol and m-hydroxyphenylpropanoic acid[220]. Similarly, metabolites of verbascoside by intestinal bacteria *in vitro* were also identified by another two studies[221,222]. The metabolites may lead to the low bioavailability of verbascoside *in vivo*.

The metabolism of echinacoside in human fecal microbial in vitro showed that the deglycosylation,

reduction, hydroxylation, dehydroxylation, and acetylation were the main pathways to generate 13 echinacoside metabolites. The metabolites mainly include verbascoside, caffeic acid, hydroxytyrosol, m-hydroxyphenylpropanoic acid, and dihydrocaffeic acid[223]. Only caffeic acid, hydroxytyrosol and dihydrocaffeic acid were found in the metabolites of forsythoside A by human intestinal bacteria *in vitro*. It was proposed that caffeic acid was produced by hydrolyzing forsythoside A, and was hydrogenated further to form 3,4-dihydroxybenzenepropionic acid[224].

Eleven metabolites of verbascoside, seven metabolites of isoverbascoside, and 11 metabolites of 2-acetylverbascoside generated by gut microbiota were found via metabolic pathways including deglycosylation, deacetylation, dehydroxytyrosol, decaffeoyl, acetylation, reduction, and sulfate conjugation[225]. All the intermediates of verbascoside and isoverbascoside produced by gut microbiota were transformed to 3-hydroxyphenylpropionic acid and hydroxytyrosol after 48 h incubation, which is in consistent with the echinacoside microbial metabolisms[223]. Li et al. confirmed that PhGs were more likely to be biotransformed to their caffeic acid and aglycones derivatives via glucuronidation and deglycosylation and by human intestinal bacteria in vitro[226]. However, only 30% of echinacoside from the *C. tubulosa* extract was metabolized after incubated with gut microbiota for 48 h, while another research demonstrated that echinacoside was completely metabolized after incubation with gut microbiota for 48 h[223]. The difference in the metabolism of single compound and the *C. tubulosa* extract was probably because of the presences of oligosaccharides and polysaccharides in the plant extract.

7. Bioactivities of PhGs metabolites

As mentioned in section 2, PhGs exhibit extensive strong activities. However, clear pharmacological characteristics such as poor absorption, extensive and fast metabolism in the gut, liver and blood, lead to their extremely low bioavailability of PhGs. Thus, there is some controversy with regard to whether PhGs themselves are the primary compounds contributing significantly to the beneficial activities, or whether the activity of their metabolites are responsible for the biological activities.

It is worth noting that the main and common degradation products of PhGs, such as caffeic acid and hydroxytyrosol, and the derivatives of caffeic acid and hydroxytyrosol, are reported to possess potent antioxidant with many health benefits [227, 228]. The antioxidant activity of several PhGs, caffeic acid-related metabolites, and hydroxytyrosol-related metabolites were evaluated by the DPPH assay[229]. The metabolites showed stronger activity than PhGs. Their antioxidant activity decreased in the following order: ferulic acid (hydroxytyrosol-related), 3,4-dihydroxybenzenepropanoic acid (caffeic acid-related), caffeic acid,

tubuloside B, verbascoside, isoverbascoside, tubuloside A, poliumoside, hydroxytyrosol and echinacoside with the IC_{50} values of 1.312, 1.556, 1.601, 2.469, 3.166, 3.235, 3.452, 3.613, 3.952 and 4.799 μg/mL, respectively[229]. It has also been reported that caffeic acid and hydroxytyrosol were more active than verbascoside and isoverbascoside in antiprotein glycation activities *in vitro*[230]. The antimicrobial activity of forsythoside A, and its metabolites such as caffeic acid, hydroxytyrosol and 3,4-dihydroxybenzenepropionic acid (DCA) was evaluated using the agar well diffusion method in vitro. Caffeic acid has no activity, and hydroxytyrosol displayed the highest antimicrobial activity, followed by forsythoside A and DCA. The MIC values of forsythoside A, hydroxytyrosol and DCA against *S. aureus* are 25, 50 and 50 μg/mL, respectively[224]. The antiendotoxin activities of forsythoside A, caffeic acid, hydroxytyrosol and DCA were determined by the LAL assay *in vitro*. The results showed forsythoside A and caffeic acid were invalid even at the maximal concentration (1000 μg/mL). While hydroxytyrosol and DCA were still effective when diluted four and three times, respectively[224]. It was found that verbascoside metabolites such as hydroxytyrosol, caffeic acid and 3-hydroxyphenylpropionic acid (3-HPP), possessed higher hepatoprotective activities than verbascoside through regulating oxidative stress, lipid peroxidation, and inflammatory responses in a GalN/LPS induced acute hepatic-injury mouse model at the dosage of 0.15 mmol/kg[231]. In addition, dihydrocaffeic acid exhibited protective activities on ischemia-induced neuronal damage and brain edema cerebral on a focal cerebral ischemia rat model[232]. Besides, m-hydroxyphenylpropanoic acid displayed antioxidant effect[234] and decaffeoyl verbascoside possessed anti-inflammatory activity in *vivo and vitro*[233]. Therefore, we can make the conclusion that the metabolites of PhGs such as hydroxytyrosol, caffeic acid, 3-HPP, DCA, decaffeoyl verbascoside and m-hydroxyphenylpropanoic are the active substances *in vivo*.

Further comparative studies would be of great value, to confirm whether the administration of PhGs metabolites is more beneficial than traditional PhGs administration. Even if PhGs metabolites showed promising acvities when tested alone *in vivo* and *in vivo*, whether the concentration of metabolites can reach the concentration that make it effective in *vivo* needs to be carefully considered. Thus, strategies to enhance the bioavailability of PhGs are still highly significant.

8. Approaches to improve the bioavailability of PhGs

Numerous approaches such as bioenhancers, β-cyclodextrin encapsulation, liposomal PhGs, nanoparticles and phospholipid complex have been applied to improve the bioavailability of PhGs (Figure 7).

8.1 Bioenhancers

Low intestinal absorption is one of the most important factors causing the low bioavailability of PhGs.

Some plant essential oils such as borneol, pennyroyal and clove oil could act as absorption promoters to improve intestinal absorption of active compounds[235, 236]. Moreover, some efflux proteins such as P-glycoprotein (P-gp) belonging to ATP-binding cassette transporters superfamily, and multidrug resistance protein (MRP) are abundant in the human intestines, and play a significant role in drug absorption, transport, and bioavailability[237, 238]. Efflux protein inhibitors are potential to enhance the bioavailability of several important anticancer drugs (anthracyclines, taxanes, etc.) by occupying the drug binding sites as a competitive blocker, binding chemosensetizer sites as a non-competitive antagonist, altering P-gp expression or inhibiting the ATPase function and related proteins[239, 240].

Several bioavailability enhancers have been applied to improve the bioavailability of PhGs. The addition of 320 μM epigallocatechin gallate (EGCG) significantly increased the Papp(AP → BL) value of verbascoside (320 μM) to 5.69×10^{-7} cm/s in Caco-2 monolayers. Further pharmacokinetics study of verbascoside in rats demonstrated that after oral administration of 200 mg/kg verbascoside and 200 mg/kg EGCG, the AUC of verbascoside was increased to 1.43 fold that of pure verbascoside[241]. It was shown that the Papp value of forsythoside A *in vitro* Caco-2 monolayer model was significantly increased to 208% and 206% by 32 μg/mL water-soluble chitosan and 80 μg/mL sodium caprate, respectively. Pharmacokinetics study of forsythoside A in rat showed that $AUC_{0–480\ min}$ (ng min/mL) of forsythoside A, forsythoside A with 100 mg/kg sodium caprate, and forsythoside A with 50 mg/kg water-soluble chitosan was 6396.5, 11041 and 12412.7, respectively[242]. A similar research also demonstrated that the absorption of forsythoside A in SHL was increased by absorption enhancers such as water-soluble chitosan and sodium caprate[242]. 10, 32 and 250 μg/mLwater-soluble chitosan increased the Papp value to 119%, 206% and 165% in Caco-2 cells[242]. And the Papp value was increased to 128%, 175% and 208% after the addition of 10, 32 and 80 μg/mL of the sodium caprate[242]. 100 mg/kg sodium caprate and 50 mg/kg water-soluble chitosan increased the AUC_{0-t} from 6396.5 ng min/mL to 11041.5 and 10597.0 ng min/mL, respectively, in rats[242].

The P_{app} values of forsythoside B, isoforsythoside, and forsythoside A were significantly improved to 1282%, 989.6%, and 561.0% with the addition of 0.1% chito-oligosaccharide (COS)[243]. The C_{max} values of isoforsythoside, and forsythoside B, forsythoside A were increased to 214%, 185.4%, and 161%, respectively. Besides, the AUC values of forsythoside A, isoforsythoside and forsythoside B were enhanced to 290%, 252% and 214%, respectively, after the addition of 25 mg/kg COS[243]. The C_{max} values of 0.09 mg/mL echinacoside + 0.1 mg/mL clove oil and 0.09 mg/mL echinacoside + 0.1 mg/mL verapamil were about 2.58 fold and 1.4 fold higher than of echinacoside alone. And the oral bioavailability of echinacoside (120 mg/kg) in rats administrated with clove oil (0.1 ml/mL) and verapamil (0.2 mg/mL) were significantly

improved by 2.36 fold and 1.37 fold, compared with echinacoside alone[200].

8.2 Different matrix

The activity and bioavailability of bioactive component can be influenced by the complex chemicals in compound prescriptions. Zhou et al. investigated the pharmacokinetics of forsythoside A in different combinations of SHL, *Scutellariae radix* (SR), *Japonicae flos* (LJF), and *F. fructus* (FF). Compared with FF, C_{max} of forsythoside A in SHL, FF+SR and FF+LJF was increased from 9.830 ng/mL to 30.559, 24.39 and 15.97 ng/mL, respectively. And $AUC_{0\rightarrow1440}$ of forsythoside A in SHL, FF+SR and FF+LJF were prolonged from 1.210 μg min/mL to 6.879, 3.758, and 3.678 μg min/mL, respectively[244]. In the research of Tanino et al., the dietary of *C. tubulosa* extract enhanced the intestinal absorption of verbascoside and echinacoside to almost three times than pure verbascoside and echinacoside[245]. Similarly, another study showed that some pharmacokinetic parameters of salidroside after p.o. administration of *Rhodiola. crenulata* extract (at a dose containing salidroside 46.2 mg/kg) were not equal to those of pure salidroside. Salidroside in plasma can still be detected after 24 h of oral administration of the *R. crenulata* extract. The $T_{1/2}$ value of salidroside was 7.91 h, which is much larger than that of pure salidroside (1.1 h)[194]. The increased bioavailability maybe caused by the following reasons. Firstly, other complex constituents in the matrix of PhGs promoted the absorption of PhGs, and thus increased the bioavailability. Secondly, other compounds were metabolized into compounds with the same m/z as PhGs *in vivo*, and thus the concentration of PhGs was increased. In addition, different dosage could also lead to the observed differences in pharmacokinetic parameters of PhGs.

8.3 β-Cyclodextrin encapsulation

Sheng et al. found the benzene ring of echinacoside can enter into the cavity of β-CD to form echinacoside-β-CD complex, which provided a distinctive method to improve water solubility and thermal stability of echinacoside[246]. Stability studies made by nuclear magnetic resonance showed that verbascoside enclosed in β- CD complex was more stable than that of free verbascoside[247]. Verbascoside induced proton shifts and intermolecular ROE signals demonstrated that the caffeoyl moiety of verbascoside is deeply inserted in the cyclodextrin cavity[247]. It has been reported that the inclusion complex of β-CD and forsythiaside can significantly decrease the degradation degree of forsythiaside compared with free forsythiaside[248]. Under sunshine conditions, almost 90% forsythiaside was degraded after 100 h, while almost 45% of forsythiaside was still remained in forsythiaside inclusion complex[248]. Forsythiaside A was suffered from a degradation

of 11.47% under 75% relative humidity after 10 days. β-CD complex form can significantly improve the stability of forsythiaside A, with the degradation rate of only 4.57% under the same conditions. Under a strong light of 4500 ± 500 Lx, 29.23% of forsythiaside A was degraded, while forsythiaside A was degraded 15.56% in inclusion complex[249]. Besides, forsythiaside A/β-CD complex showed higher scavenging free radical ability than forsythiaside A. The IC_{50} of forsythiaside A/β-CD complex and forsythiaside A were determined as 6.2×10^{-6} and 4.2×10^{-6} M, respectively[249].

8.4 Nanotechnology

Nanotechnology is currently one of the hot fields in pharmaceutical research and it has been applied to increase the clinical efficacy of natural products. Nanoparticles have been shown to increase the bioavailability of natural products, by improving the compound's stability within biological systems. Preventing natural products from rapid metabolization in the gastrointestinal tract and liver is also one general mechanism that can increase the bioavailability. In addition, nanoparticles can increase the solubility and transport across membranes of active compounds[250].

8.4.1 Liposomes

Isacchi et al. developed and optimized the unilamellar liposomes loaded with verbascoside and tested its advantage in improving the stability and bioavailability of verbascoside. It was demonstrated that liposome was a suitable deliver to enhance the stability and efficiency of verbascoside. Liposomes can prevent the hydrolysis of verbascoside resulting in caffeic acid oxidation. 91% of verbascoside remained in the liposomes after 3 months. In addition, verbascoside liposomes (i. p., 100 mg/kg) showed a prolonged anti-hyperalgesic activity compared with the pure verbascoside in rats at the same dose[251]. Zhao et al. compared the pharmacokinetics and tissue distribution of forsythiaside liposomes (20 mg/kg) and forsythiaside solution (20mg/kg) in chicks by intravenous administration. Compared with forsythiaside solution, the forsythiaside distribution in liver, spleen and lung were obviously increased in forsythiaside liposome. The concentration of forsythiaside in plasm was 14.42 10.72 and 3.70 μg/mL at 5 min, 10 min and 5min, respectively, for pure forsythiaside, while that for forsythiaside liposome was 35.98, 23.77, and 14.65 μg/mL, respectively. The forsythiaside liposome could increase the $T_{1/2}$ from 0.11h to 1.79 h, and increase the AUC from 4.26 μg·h/mL to 39.95 μg·h/mL, thus prolonged the drug effect time of forsythiaside in the blood circulating system[252]. Release experiments indicated that the amount of salidroside released from salidroside liposome was significantly decreased[253]. Another experiment showed that salidroside liposome can enhance the plasma concentration and slow down the release rate, thus leading to an increase of its oral

bioavailability to 1.77 times in rats[254]. The activity of promoting skin repair and ameliorating skin inflammation of verbascoside suggests its potential application for cutaneous topical application. It has been reported that verbascoside liposome can not only increase the stability, but also promote verbascoside accumulation into the stratum corneum[255] and improve the efficacy of a verbascoside based liposomal eyedrops[256]. Moreover, salidroside liposome formulation can be used in vaccine delivery systems to realize the controlled release of salidroside[257].

8.4.2 Improved liposomes

Peng et al. investigated different delivery systems for controlled release of salidroside and found that the new polymeric liposomes based on amphiphilic chitosan derivatives (DC-Ls) showed better encapsulation potential and slower sustained release rates of salidroside than traditional liposomes (phosphatidylcholine/cholesterol liposomes, PC-Ls)[258]. the release rate was 82.33% and 66.98% for PC-Ls and DC-Ls after 50 h, respectively. Zhou et al. prepared a series of liposomes such as verbascoside liposome (Ac-Lip), verbascoside/EGCG liposome (AE-Lip), chitosan-coated liposomes (CS-Ac-Lip, CS-AE-Lip) and chitosan-coated liposome tripolyphosphate particles (CS-Ac-Lip-TPP, CS-AE-Lip-TPP). The highest entrapment efficiency was found in CS-Ac-Lip-TPP with the value of 92.74%. CS-AE-Lip-TPP enhanced the bioavailability of verbascoside to 5.32 times, and increased verbascoside contents in different tissues in rats[259]. After p.o. administration of 200 mg/kg verbascoside to rats, the C_{max}, T_{max}, $T_{1/2}$, and AUC were 0.44 μg/mL, 0.54 h, 1.83 h and 1.26 μg·h/mL, respectively. While these values for CS-Ac-Lip (200 mg/kg verbascoside content) were 0.76 mg/mL, 1.92 h, 5.16 h, and 5.58 μg·h/mL, respectively[259]. Li et al. prepared a form of cistanche PhGs (CPhGs) liquid proliposomes (CPhGsP). The CPhGsP showed higher encapsulation efficiency and was more stable than CPhGs ordinary liposomes. The plasma levels of echinacoside in rabbits administrated with CPhGsP (25 mg/kg) were higher than those with CPhGs (25 mg/kg) at 5, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240 and 360 min. The C_{max} and T_{max} values of proliposomes were 324.23 ng/mL and 30 min, respectively, while that of CPhGs was 193.17 ng/mL and 15 min respectively. Besides that, $AUC_{0-\infty}$ values for CPhGsP group (15494 ng·h/mL) was also higher than CPhGs (24552.14 ng·h/mL). The oral bioavailability of CPhGs was significantly increased by the proliposome formulation, which offers a novel strategy to prepare liposomes for orally administrating of PhGs[260].

8.4.3 Other nanoparticles

Cadmium telluride quantum dots (QDs) have attracted the attention of biomedical researchers as they can be used as a novel drug delivery system. Verbascoside as a chemotherapeutic agent was successfully fixed into QDs through covalent bonding between the OH group of verbascoside and the COOH group of QDs[261]. Treatment of QDs together with verbascoside in HepG2/ADM cells caused the apoptosis rate to 90%, much higher than that treatment with verbascoside alone (45%). Besides, verbascoside QDs effectively inhibited the human HepG2 hepatoma cells growth in mice[261]. Multifunctional verbascoside coated Ni nanoparticles[262] and Au nanoparticles[263] have also been reported to effectively inhibit the growth and induce the apoptosis of tumor cells *in vitro* and *in vivo*.

To improve the stability and enhance the bioavailability of echinacoside, poly (lactic-co-glycolic acid) PLGA encapsulated echinacoside was prepared. The in vitro release experiment showed that PLGA-echinacoside released 60% while the pure echinacoside released 90% after four h[264]. Salidroside-chitosan nanoparticles (SA-CS-NPs) showed sustained release properties with the maximum release rate of 86.55% after 24 h, while pure salidroside reached the maximum release rate in one hour[265]. Furthermore, pH-sensitive nano-carrier provides another platform to improve the bioavailability of drugs. Peng et al. prepared a new pH-sensitive nano-carrier with poly (acrylic acid) (PAA) as shell-layers and mesoporous silica nanoparticles (MSNs) as cores to realize the sustainable release of salidroside. PAA layers had the characteristic of showing closed and opened states in response to different pH values, and thereby regulated the release and uptake of salidroside[266].

Salidroside has been demonstrated to possess skin protective effects, but the hydrophilicity of salidroside cause its poor permeability and absorption[267]. A nanosphere-gel delivery system exhibiting controlled release of paeonol and salidroside was successfully prepared. Compared with treatments of paeonol-loaded nanosphere dispersion and salidroside-loaded hydroge, the nanosphere-hydrogel formulation with paeonol and salidroside decreased the melanin levels to a larger extent in guinea pig skin induced by ultraviolet B[268]. Besides that, niosomes were also applied as transdermal nanocarriers in salidroside to enhance its transdermal delivery[269]. Niosomes have the advantage of less susceptible to oxidation, more stable, and less costly[270]. The bioavailability of topically administrated drugs can be improved by niosomes through increasing the skin permeability[271]. Zhang et al. prepared niosomes loaded with salidroside and investigated its uptake in two kinds of skin cells. The niosomal formulations delivered more amount of salidroside (2.3 times) across the skin than that in aqueous solution[272].

8.5 Other methods

As liposomes exhibit many disadvantages mentioned above, and silica nanoparticles cannot be employed in drug and functional food industries, formulating novel systems for PhGs encapsulation may be an effective way to overcome these problems. Microsphere delivery systems based on natural polymer, such as zein, gelatin, and chitosan microsphere, have attracted widespread attention as they are non-toxic, well biocompatibility, and biodegradability[273-275]. Luo et al. demonstrated the potential of genipin crosslinked salidroside chitosan in the application of delivering salidroside. They successfully prepared salidroside-chitosan microspheres using genipin which showed less cytotoxicity as a crossing agent. The salidroside stability was improved after being entrapped into chitosan microspheres. The release rate of salidroside from chitosan microspheres was rapid initially, followed by controlled release[276]. Improved stability and controlled release of salidroside were also achieved through incorporation of salidroside into polymer network microspheres prepared by chitosan and methylcellulose[277].

To enhance the intestinal absorption and oral bioavailability, echinacoside-phospholipid complex was prepared. Compared with echinacoside alone, the echinacoside phospholipid complex could significantly increase the absorption rate and P_{eff} to 2.82 fold and 3.39 fold, respectively. Besides, the echinacoside phospholipid complex could increase the C_{max} and AUC_{0-1} to 2.5 and 2.1 times, respectively[278].

9. Perspectives

Almost 50 years have passed since the isolation of the first PhGs, and plenty of experimental data have demonstrated the potent pharmacological activities of PhGs. However, many issues remain unresolved concerning their effective applications in clinic at present. Firstly, of all the over 572 compounds, reported pharmacological studies only focused on limited number of compounds such as salidroside, verbascoside, echinacoside, forsythoside, and isoverbascoside. Other compounds exhibiting excellent pharmacological activities should also be investigated in depth. And also, 1310 articles about PhGs have been published so far, but 612 of them are from China, followed by Japan (144), Turkey (111), USA (55) and Italy (51). It is necessary to attract the attention of pharmacologists from other countries to carry on researches in PhGs. Another important aspect is that the mode of action and the structure activity relationships of PhGs are still not quite clear. Besides, although a large number of laboratory data illuminate the therapeutic effect of PhGs in various diseases, detailed clinical data are still quite limited. It is expected that the therapeutic potential of PhGs will be further explored with more PhGs identified, the further clarification of the mechanism of action and structure-activity relationships, as well as more clinical trials carried out on the safety and efficiency of PhGs. In addition, many factors such as different processing methods, different food matrix,

bio-encapsulation, as well as the addition of lipids can influence the bioavailability of PhGs. Thus, detailed relevant researches are required to identify the optimum conditions to improve the bioavailability of PhGs. What is more, although the present article summarized the different approaches to increase the bioavailability and efficacy of PhGs in different experimental models, studies about improving PhGs bioavailability and efficacy have not been conducted in human. Therefore, further research to enhance the bioavailability of these valuable phytochemicals are needed for human use.

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Author's biosketches

Lipeng Wu obtained his bachelor degree from Henan University of Science and Technology (2011), and master degree from Northwest Agricultural and Forestry University (2014). After that, he worked in Institute of Quality Standard and Testing Technology for Agro-Products, Xinjiang Academy of Agricultural Sciences. He became a PhD candidate in Zhejiang University in September 2018. Ever since, the neuro-protective activity of phenylethanoid glycosides has been Mr. Wu's main research focus.

Milen I. Georgiev holds a PhD in biotechnology from the Stephan Angeloff Institute of Microbiology (Bulgarian Academy of Sciences). He has the research focus of phenylethanoid glycosides for 10+ years. He serves as the associate editor of *Phytomedicine* and *Food and Chemical Toxicology,* and the editorial boards of *Biotechnology Letters* and *Chinese Medicine*. He was the Chairman of International Conference on Natural Products Utilization International Conference on Natural Products Utilization, From Plants to Pharmacy Shelf. He has 15 years of experience in natural products field and has published in excess of 120 papers. He has delivered 50+ invited lectures in 20 different countries. His current research focuses on the biosynthesis of fine molecules and the development of biotechnological tools for their sustainable mass production along with the application of emerging platforms for comprehensive metabolite profiling and biochemometrics. Milen holds several grants from the NSF of Bulgaria and framework programmes of European Union (incl. H2020 – PlantaSYST project, well-funded with €15M). At present, he coordinates the project SusMAPWaste @ USAMV in Bucharest (Romania).

Hui Cao received her Ph.D. in Analytical Chemistry at Central South University, China in 2015. During her Ph.D. period, she spent two years to study at the University of Würzburg, Germany. Following two

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Hesham R. El-Seedi is working in the area of isolation, structure elucidation and synthesis of biologically active natural products from medicinal plants, marine and bee products. Prof. Hesham is a former fellow of the Japanese Society of Promotion of Science (JSPS), Faculty of Science and Technology, Keio University, Japan, under direction of Prof. Shosuke Yamamura and Prof. S. Nishiyama. Throughout his carrier, he worked in pioneer internationally recognized laboratories including Geneva University, Switzerland, in collaboration with Prof. Kurt Hostettmann, Kunglia Tekniska Högskola (KTH), Stockholm, Sweden (since 2007), Faculty of Pharmacy, Uppsala Biomedical Center, Uppsala University, Sweden and Menoufia University, Egypt. He was appointed as Adjunct Faculty Professor at the International Center for Chemical and Biological Sciences (ICCBS), Karachi, Pakistan, 2017 and was rewarded two Swedish Research Links grants for the 2017-2019. He has published peer-reviewed international research articles and scientific papers, reviews, chapters in Peer-Reviewed International Journals. He has presented his research at several scientific conferences worldwide. For many years of Scientific Contributions to

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Satyajit D. Sarker obtained his BPharm (Hons) and MPharm (postgraduate) degrees from the University of Dhaka, and secured first class first position in order of merit in both programmes. He completed his PhD in Pharmaceutical Sciences from the University of Strathclyde, under the supervision of one of the pioneers in phytochemistry research in the UK, Professor Peter G Waterman, and also Professor Alexander I Gray. He is a Professor of Pharmacy, and has been the Director of the School of Pharmacy and Biomolecular Sciences at the Liverpool John Moores University (LJMU) since 2013. Prior to the current post, he had worked as a Professor of Pharmacy, Deputy Head of Pharmacy and Pharmacy Research Group Leader at the University of Wolverhampton during 2008-2013. He is a well-trained, highly experienced, outstandingly productive, and highly cited internationally known accomplished pharmaceutical, medicinal and natural products chemist, with more than three decades of postgraduate research experience, and 580 publications to his credit. Total Google Scholar citations was over 15,000, and h-index was 56. Prof Sarker served as the Editor-in-Chief of the Wiley journal, *Phytochemical Analysis* in 2010. He is currently in the editorial board of >30 international journals. His research is broadly in the area of pharmaceutical and natural products chemistry as well as in the area of rational drug design (medicinal chemistry). His research focuses on anticancer, analgesic, anti-inflammatory, antioxidant and antimicrobial properties (against multiple-drug-resistant bacterial strains, e.g. MRSA) of purified compounds from higher plants as well as novel synthetic organic compounds.

Jianbo Xiao earned his PhD in nutritional science from Okayama Prefectural University, Japan (2009). He worked as Humboldtian at University of Wuerzbug, Germany (2013-2015), prior to join University of Macau in 2015. Prof. Xiao is currently the Editor-in-Chief of a newly launched *e-Food journal* and *Food Frontiers* (Wiley), the associate editor of *Phytochemical Analysis* (Wiley) and *Journal of Berry Research* (IOS), and in the editorial boards of several international journals, including *Critical Reviews in Food Science and Nutrition*, *Food Chemistry*, *Food and Chemical Toxicology*, *Phytomedicine*, *Industrial Crops and Products*, *International Journal of Molecular Sciences*, *Molecules*, *Environmental Toxicology and Pharmacology*, *Current Drug Metabolism*, *Anti-Cancer Agents in Medical Chemistry*, and so on. He was the chairman of 2015 International Symposium on Phytochemicals in Medicine and Food (1‐ISPMF2015) organized by PSE and its second edition (2‐ISPMF 2017), third edition (3‐ISPMF 2018). Prof. Xiao have published and accepted 171 scientific articles on peer-reviewed journals, and 101 of them were as corresponding author and first author. And 28 papers have been selected as ESI highly cited papers. The

total cited times of these papers are 5528 with h index=40 (Google, 02/27/2019), and 3859 with h index=34 (Web of Science, 02/27/2019). In addition, he has been selected as 2016, 2017 and 2019 Clarivate Analytics Highly Cited Researcher (HCR).

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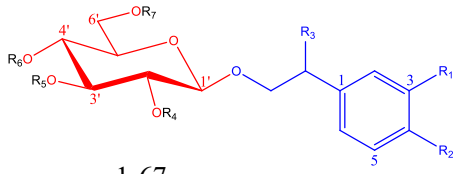
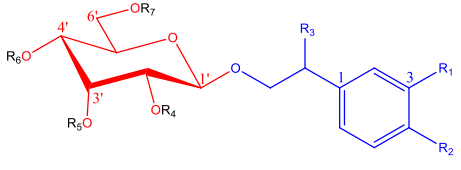
Table 1. 101 of the 111 PhGs that have not been summarized before



1-67



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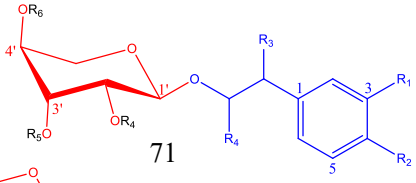

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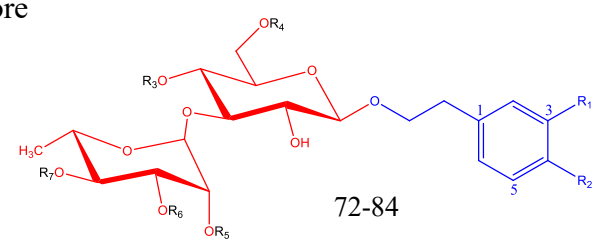

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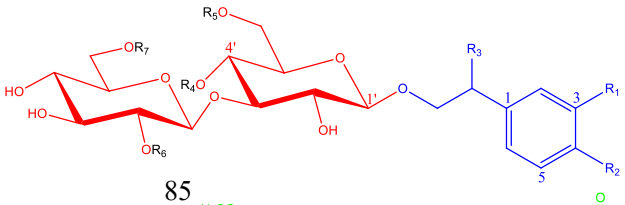

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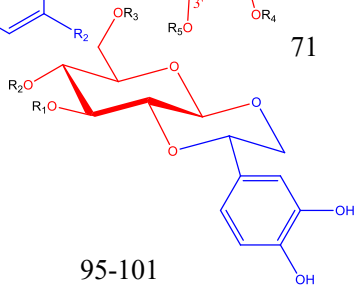
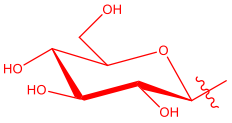
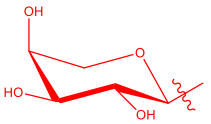
86-94



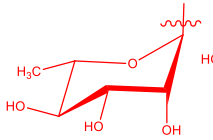
95-101



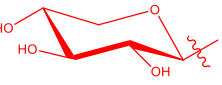
Glc



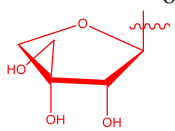
Ara



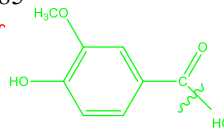
Rha



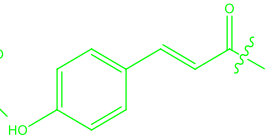
Xyl



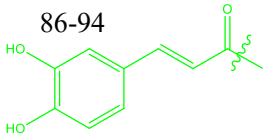
Api



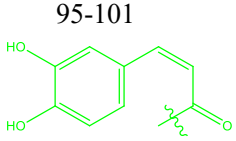
Vanilloyl



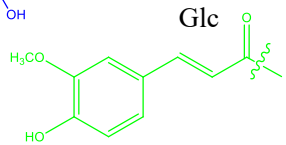
Coumaroyl



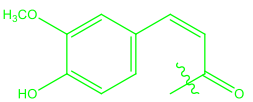
Caffeoyl



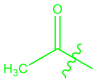
cis-Caffeoyl



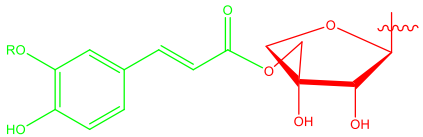
Feruloyl



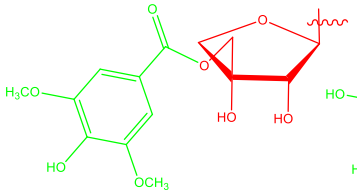
cis-Feruloyl



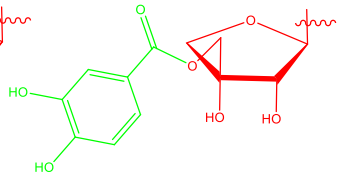
Acetyl



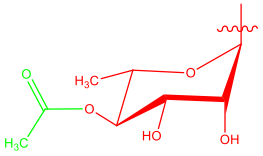
A1: R=H, A2: R=CH_3



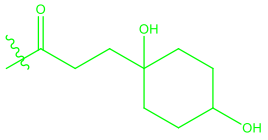
A3



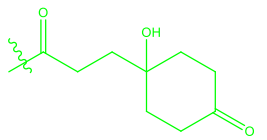
A4



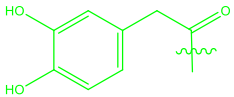
B



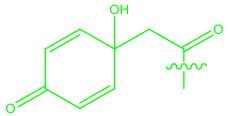
D1



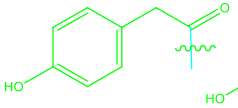
D2



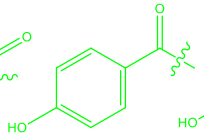
D3



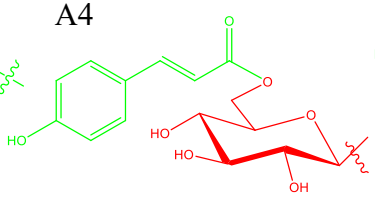
D4



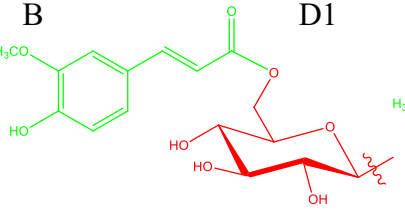
D5



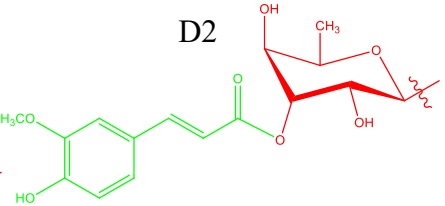
D6



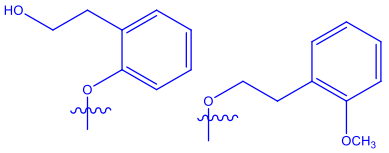
E1



E2

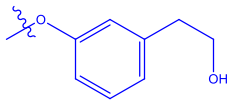


E3

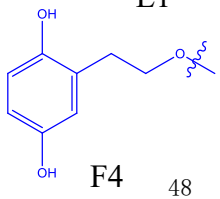


F1

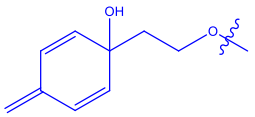
F2



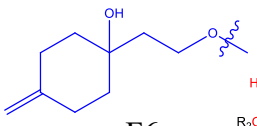
F3



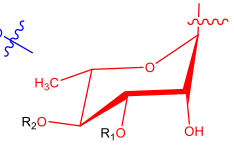
F4



F5



F6



G1:R1=H, R2=Fer
G2:R1=H, R2=Caf
G3R1=Caf, R2=H

No.	Compounds	R1	R2	R3	R4	R5	R6	R7	Source	Bioactivity	Ref
1	Osmanthuside H	H	OH	H	H	H	H	Api	*Osmanthus asiaticus*	ND[a]	11
2	Osmanthuside I	H	OH	H	H	H	H	A1			
3	Osmanthuside J	H	OH	H	H	H	H	A2			
4	ND[a]	OH	OH	OH	H	Rha	H	Feru	*Sesamum indicum*	ND[a]	12
5	Lipedosides A-I	OH	OH	H	H	Rha	Cou	H	*Ligustrum pedunculare*	ND[a]	13
6	Lipedosides A-II	OH	OH	H	H	Rha	H	Cou			
7	ND[a]	OH	OCH_3	H	Ara	Glc	H	Van	*Veronica undulata*	ND[a]	14
8	2-O-acetyl-3‴-O-methylverbascoside	OH	OH	H	Ace	Rha	Van	H	*Penstemon crandallii*	ND[a]	15
9	2,4″-di-O-acetyl-3‴-O-methylverbascoside	OH	OH	H	Ace	B	Van	H			
10	Betonyosides A	OH	OH	OH	H	Rha	Fer	H	*Stachys officinalis*	ND[a]	16
11	Betonyosides D	OH	OCH_3	H	H	Rha	*cis*-Fer	Api			
12	Betonyosides E	OH	OH	H	H	Rha	Fer	Api			
13	Betonyosides F	OH	OCH_3	H	H	Rha	*cis*-F	H			
14	2-(3-hydroxy-4-methoxy-phenyl)-ethyl-O-(α-l-rhamnosyl)-(1→3)-O-(α-l-rhamnosyl)-(1→6)-4-O-E-feruloyl-β-d-glucopyranoside	OH	OCH_3	H	H	Rha	Fer	Glc	*Digitalispurpurea* and *Penstemonlinarioides*	PKCα-Inhibitory	17
15	Scrosides B	OH	OCH_3	H	H	Glc	H	Fer	*Picrorhiza scrophulariiflora*	ND[a]	18
16	Scrosides C	OH	OCH_3	H	H	Glc	Fer	H			

17	ND[a]	H	H	H	H	Rha	Caff	Cou	*Globularia alypum*	ND[a]	19
18	Lophanthoside A	OH	OCH_3	H	Ace	Rha	H	H	*Rabdosia lophanthoides*	ND[a]	20
19	ND[a]	OH	OH	H	H	Rha	Caf	D1	*Jacaranda caucana*	ND[a]	21
20	ND[a]	OH	OH	H	H	Rha	Caf	D2			
21	Isoilicifolioside A	OH	OH	OCH_2CH_3	H	Rha	H	Caf	*Paulownia tomentosa*	Anticomplement	22
22	Tazettosides D	H	OCH3	H	H	H	H	Glc	*Narcissus tazetta*	Inhibiting melanogenesis	23
23	Digicilisides A	OCH3	OH	H	H	Glc	Fer	Rha	*Digitalis ciliata*	ND[a]	24
24	Digicilisides B	OH	OH	H	Ara	Glc	Fer	Rha			
25	Digicilisides C	OH	OH	H	H	Glc	Caf	E1			
26	α-L-rhamnopyranosyl-(1↔2)-β-D- [4″-(8E)-7-(3,4-dihydroxyphenyl)-8-propenoate,1″-O-(7S)-7-(3,4-dihydroxyphenyl)-7-methoxyethyl]- glucopyranoside	OH	OH	OCH_3	Rha	H	Caf	H	*Gynura cusimbua*	Antiangiogenic	25
27	Digiviridifloroside	OH	OH	H	H	H	Caf	E2	*Digitalis viridiflora*	Antibacterial	26
28	2-(4-hydroxyphenyl)ethanol-O-β-D-glucopyranosyl-(1→2)-O-β-D-glucopyranoside	H	OH	H	Glu	H	H	H	*Sambucus williamsii*	Hepatoprotective	27
29	Forsythoside M	H	OH	H	H	H	H	Van	*Forsythia suspensa*	Hepatoprotective	28
30	Forsythoside N	H	OH	H	H	H	H	D4			
31	Forsythoside P	H	OH	H	H	H	Caf	Rha			

32	Hodgsonialloside A	OH	OCH_3	H	H	H	H	H			
33	Hodgsonialloside B	OH	OCH_3	H	H	H	Glc	H	*Magnolia hodgsonii*	ND[a]	29
34	Hodgsonialloside C	OCH_3	OH	H	H	H	H	H			
35	1-β-p-hydroxyphenyl-ethyl-2-O-acetyl-3,6-di-α-L-rhamnopyranosyl-β-D-glucopyranoside	H	OH	H	Ace	Rha	H	Rha			
36	1-β-p-hydroxyphenyl-ethyl-3,6-O-di-α-L-rhamnopyranosyl-β-D-glucopyranoside	H	OH	H	H	Rha	H	Rha			
37	1-β-p-hydroxyphenyl-ethyl-2-O-acetyl-3,6-di-α-L-rhamnopyranosyl-4-p-coumaroyl-β-D-glucopyranoside	H	OH	H	Ace	Rha	Cou	Rha	*Cistanche phelypaea*	Inhibiting Monoacylglycerol Lipase	30
38	1-β-p-hydroxyphenyl-ethyl-3,6-di-α-L-rhamnopyranosyl-4-p-coumaroyl-β-D-glucopyranoside	H	OH	H	H	Rha	Cou	Rha			
39	Ternifoliusoside F	OH	OCH_3	H	Ace	G1	Fer	H			
40	Ternifoliusoside G	OH	OCH_3	H	Ace	G1	H	Fer	*Isodon ternifolius*	Antiinflammatory	31
41	Ternifoliusoside H	OH	OCH_3	H	Ace	Rha	H	Fer			
42	Lippiarubelloside A	OH	OH	H	H	G2	Caf	H	*Lippia rubella*	Antifungal	32
43	Lippiarubelloside B	OH	OH	H	H	G3	Cou	H			
44	Digidavisoside A	OH	OCH_3	H	H	Glc	Caf	Glc			
45	Digidavisoside B	OH	OCH_3	H	H	Glc	Fer	Glc	*Digitalis davisiana*	Cytotoxic	33
46	Davisoside	OH	OH	H	H	Glc	Fer	Rha			

47	3,4-dihydroxyphenyl)ethyl 2-O-[5-O-(4-hydroxy-3,5-dimethoxybenzoyl)-β-D-apiofuranosyl]-β-D glucopyranoside	OH	OH	H	A3	H	H	H			
48	3,4-dihydroxyphenyl)ethyl 2-O-[5-O- (3,4-dihydroxybenzoyl)-β-D-apiofuranosyl]-β-D-glucopyranoside	OH	OH	H	A4	H	H	H	*Arrabidaea brachypoda*	Gastroprotective	34
49	2-(3,4-dihydroxyphenyl)-ethyl 1-O-[4-O-feruloyl-2-O-a-L-rhamnopyranosyl-3-O-a-L-rhamnopyranosyl]- β-D-glucopyranoside	OH	OH	H	Rha	Rha	Fer	H			
50	2-(3,4-dihydroxyphenyl)-ethyl1-O-[4-O-coumaroyl-2-O-a-L-rhamnopyranosyl-3-O-a-L-rhamnopyranosyl]-β-D-glucopyranoside	OH	OH	H	Rha	Rha	Cou	H	*Euphrasia rostkoviana*	ND[a]	35
51	Steviophethanoside	H	OH	H	H	H	H	Ara	*Stevia rebaudiana*	Antidiabetic	36
52	ND[a]	H	H	H	H	Glc	Caf	H	*Plantago depressa*	Antiradical	37
53	Terngymnosides A	OH	OH	H	D3	H	H	D4			
54	Terngymnosides B	OH	OH	H	D5	H	H	D4	*Ternstroemia gymnanthera*	Analgesic	38
55	Terngymnosides C	OH	OH	H	H	H	H	D4			
56	Terngymnosides D	OH	OH	H	F1	H	H	D3			
57	Nepetifosides D	OH	OH	OCH3	H	Rha	Fer	Api			
58	Nepetifosides F	OH	OH	$O(CH2)_3CH_3$	H	Rha	Caf	Api	*Schnabelia nepetifolia*	Osteoblast proliferation	39

59	Flavaioside	OCH3	OH	H	H	E3	Fer	Rha	*Scrophularia flava*	Antidiabetic	40
60	Ramoside A	OH	OH	H	H	Rha	Cou	Rha	*Orobanche caryophyllacea*	Antioxidant	41
61	2′-acetylramoside A	OH	OH	H	Ace	Rha	Cou	Rha			
62	Rostkovianoside	OH	OH	H	Rha	Rha	H	H	*Euphrasia rostkoviana*	ND[a]	42
63	6′-O-acetylcrassifolioside	OH	OH	H	Rha	Rha	Caf	Ace			
64	Macrophylloside E	H	H	H	H	Rha	H	Caf		ND[a]	43
65	Macrophylloside F	OH	OH	OH	OH	Rha	H	Caf			
66	Ginkgoside C	OH	OH	H	Glc	H	H	H	*Ginkgo biloba*	Tyrosinase inhibitory	44
67	Ginkgoside D	OH	OH	H	H	Glc	H	H			
68	Sanangoside	OH	OH	H	H	Caf	H	H	*Sanango racemosum*	ND[a]	45
69	2-(3,4-dihydroxyphenyl)ethyl O-A-L-rhamnopyranosyl-(1→2)-β-D-allopyranoside	OH	OH	H	Rha	H	H	H	*Marchantia polymorpha*	ND[a]	46
70	2-(3,4-dihydroxyphenyl)ethyl O-β-D-xylopyranosyl-(1→6)-β-D-allopyranoside	OH	OH	H	H	H	H	Xyl			
71	8'-(3,4-Dihydroxyphenyl)ethyl-*O*-α-L-rhamnopyranosyl-(1-4)-2-*O*-(*E*)-caffeoyl-α-L-arabinopyranoside	OH	OH	H	cis-Caf	H	Rha	Rha	*Forsythia koreana*	Neuroprotective	47
72	2‴,3‴-diacetyl-O-betonyoside D	OH	OCH_3	Fer	H	Rha	Ace	H	*Phlomis umbrosa*	ND[a]	48
73	3‴,4‴-diacetyl-O-betonyoside D	OH	OCH_3	Fer	H	H	Ace	Ace			

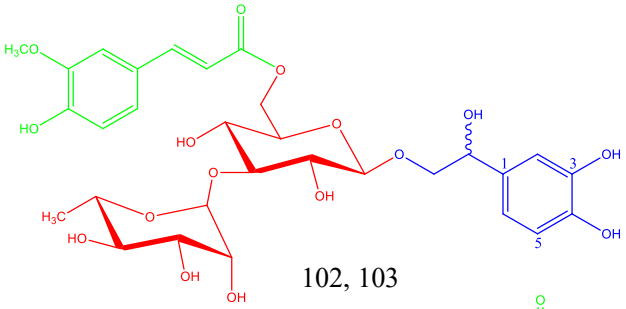
74	Ligupurpurosides C	H	OH	H	Cou	H	H	Rha	*Ligustrum purpurascens*	Antioxidant	49
75	Ligupurpurosides D	H	OH	H	Caf	H	H	Rha			
76	Barlerinoside	OH	OH	Caf	Glc	H	Rha	H	*Barleria prionitis*	Antioxidant	50
77	Nepetifosides B	OH	OCH_3	Caf	Api	H	H	H	*Schnabelia nepetifolia*	Osteoblast proliferation	39
78	nepetifosides C	OH	OCH_3	Caf	Api	H	H	Xyl			
79	Nepetifosides E	OH	OH	Caf	Api	H	H	Xyl			
80	Nepetifosides G	H	H	Caf	Api	H	H	H			
81	Nepetifosides H	OH	OCH_3	Cou	Api	H	H	H			
82	Nepetifosides K	OH	OH	H	Caf	H	H	Xyl			
83	Nepetifosides L	OH	OH	Caf	Rha	H	H	Xyl			
84	Lagotiside C	OH	OH	H	Caf	H	H	Glc	*Lagotis brachystachya*	Inhibiting Xanthione Oxidase	51
85	Scrosides A	OH	OCH_3	H	H	Fer	Glc	H	*Picrorhiza scrophulariiflora*	ND[a]	18
86	Tazettosides A	F1	H	H					*Narcissus tazetta*	Inhibiting melanogenesis	23
87	Tazettosides B	F2	H	H							
88	Tazettosides C	F2	H	Glc							
89	2-(4-hydroxyphenyl)ethanol-3-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranoside	F3	H	Glc					*Sambucus williamsii*	Hepatoprotective	27

90	Forsythoside O	F4	H	Fer			
91	Forsythenside M	F5	H	D6			
92	Forsythenside N	F5	H	Van	*Forsythia suspensa*	Hepatoprotective	28
93	Rengyoside D	F6	H	Van			
94	Rengyoside E	F6	H	Cou			
95	3′-O-methyl isocrenatoside	Rha	H	Fer	*Orobanche cernua*	Cytotoxic	52
96	Forsyoxasides A	H	Caf	Rha			
97	Forsyoxasides B	H	*cis*-Caf	Rha			
98	Forsyoxasides C	H	Cou	Rha	*Forsythia suspensa*	Neuroprotective	53
99	Forsyoxasides D	H	Caf	Xyl			
100	Forsyoxasides E	Caf	H	Xyl			
101	Forsyoxasides F	H	Caf	H			

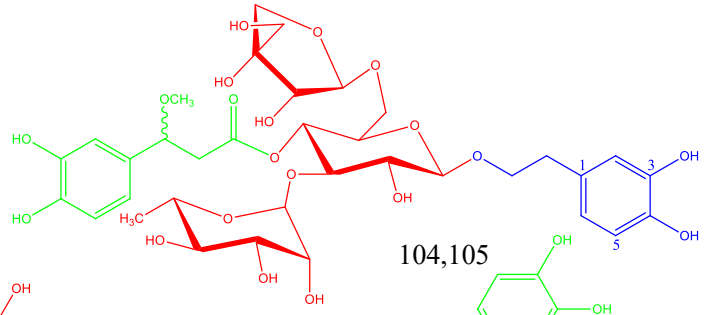
Abbreviations: ND[a]: Not determined, Glc=β-D-glucopyranose, Ara=α-L-arabinopyranose, Rha=α-L-rhamnopyranose, Xyl=β-D-xylopyranose, Api=β-D-apiofuranose, Cou=Coumaroyl, Caf=Caffeoyl, *cis*-Caf=*cis*-Caffeoyl, Ace=Acetyl, Van=Vanilloyl, Fer=Feruloyl, and *cis*-Fer=*cis*-Feruloyl.

Table 2. Ten of the 111 PhGs that have not been summarized before

No.	Compounds	Source	Bioactivity	Ref
102	Betonyosides B	*Stachys officinalis*	ND[a]	16
103	Betonyosides C			
104	Nepetifosides I	*Schnabelia nepetifolia*	Osteoblast proliferation	39
105	Nepetifosides J			
106	(7R) -campneoside I	*Magnolia sirindhorniae*	ND[a]	54
107	(7S)-campneoside I			
108	Nepetifosides A	*Schnabelia nepetifolia*	Osteoblast proliferation	39
109	Glucooleoacteoside	*Osmanthus fragrans*	Inhibit human dermal fibroblasts	55
110	Forsythenethosides A	*Forsythia suspensa*	Neuroprotective	56
111	Forsythenethosides B			

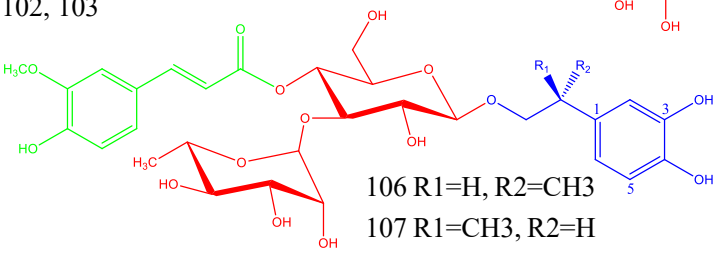


102, 103

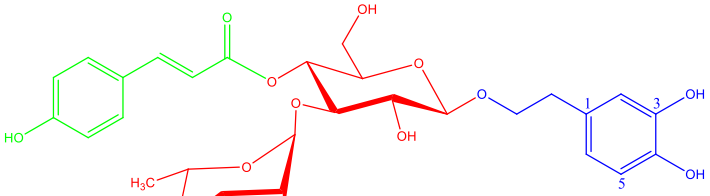


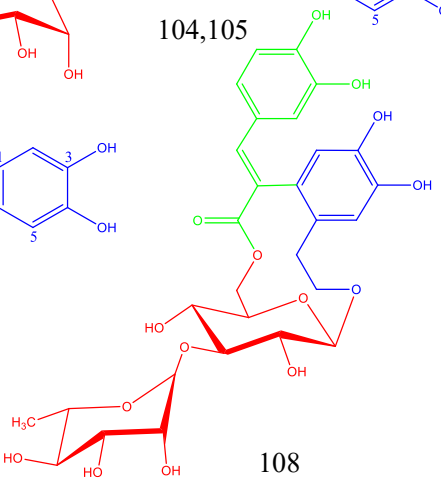
104,105

Compound 102 and 103, and compound 104 and 105 are two pairs of isomers. Compound 106 and 107 are a pair of diastereomers.

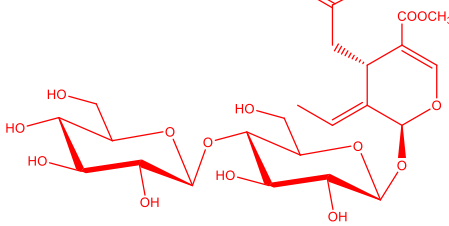


106 R1=H, R2=CH3
107 R1=CH3, R2=H





108



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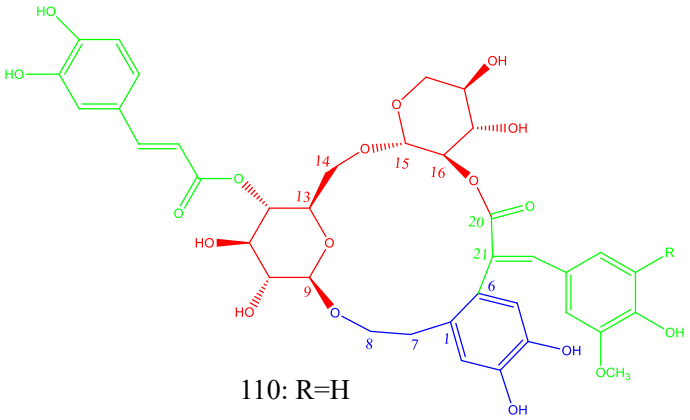

110: R=H
111:R=OCH_3

Table 3 Pharmacokinetic parameters of several PhGs

Compound	Dose mg/kg	Model	C_{max} ng/mL	T_{max} min	$T_{1/2}$ h	$AUC_{0\rightarrow t}$ ng×h/mL	$AUC_{0\rightarrow \infty}$ ng×h/mL	$MRT_{0\rightarrow t}$ h	F %	References
Verbascoside	100 p.o.	Rats	130±30	ND	1.54±0.5	ND	ND	ND	0.12	70
Verbascoside	20 p.o	Rats	162±52.6	10.2±4.8	1.49±0.28	165±21.2	181.13±20.55	1.41±0.13	1.11	189
	40 p.o		312.5±44.4	17.4±10.2	1.05±0.23	364.7±76.1	378.92±75.56	1.36±0.07	1.23	
	80 p.o		624.2±187.2	13.2±9	1.45±0.43	577.6±156.9	625.67±179.03	1.32±0.10	0.98	
Verbascoside	10 p.o	Dogs	420±100	ND	1.48±0.16	788±145.7	802.83±147.83	1.93±0.15	4.12	71
	20 p.o		720±140	ND	1.55±0.36	1464.3±131.3	1491.7±219.17	1.86±0.21	3.84	
	40 p.o		1440±240	ND	1.44±0.49	3052.3±478.2	3146.1±498.83	2.05±0.49	4.00	
Verbascoside	26 p.o.	Rats	33.2±25.8	16.7±0.23	6.08±1.25	101.29±43.85	150.38±45.14	3.34±0.76	ND	190
Forsythoside B	200 p.o.		224.6±99.2	16.4±0.28	5.00±1.21	0.19±0.08	1020.1±526.1	3.08±0.88		
Poliumoside	360 p.o.		653.5±311.9	15.8± 0.24	3.41±0.81	1211.3±926.2	1518.65±914.9	3.05±0.15		
Verbascoside	1000 p.o	Rats	1476.7±15.3	30	1.89±0.42	3.711×10^6	3710.9±173.81	2.51±0.21	ND	76
Isoacteoside			296±7	20	3.67±0.58	0.767×10^6	766.73±54.77	4.89±0.771		
Savaside A			288.3±56.1	60	1.33±0.74	0.323×10^6	322.63±135.12	1.65±0.808		
Echinacoside	100 p.o	Rats	612.2±320.4	15	1.24	1011.75	ND	ND	0.83	72
Echinacoside	10 p.o	Rats	779.2±211.7	60.0±30.0	1.1±0.3	1931.0±412.5	1982.0±420	2.1±0.4	ND	191
Salidroside	25 p.o	Rats	6493±1768	66±4.2	ND	ND	8486±2441	1.1±0.2	98	192
Salidroside	12 p.o	Rats	4300±1100	ND	ND	3376.7±1286	3416.6±1316.6	0.7±0.3	ND	193
Salidroside	46.2 p.o	Rats	3386±2138	33.6±12.6	7.91±4.42	16146±6558	18599±6529	ND	ND	194
Salidroside	100 i.g.	Rats	3716.7±860	18± 6	1.32±0.22	7552.9±549	7724.5±446.6	2.07±0.51	51.9	78
Forsythiaside	100 p.o	Rats	122.2±45.4	20.0±0.0	1.25±0.22	9508.3±1156	9513.3±1153.3	ND	0.5	73
Poliumoside	200 p.o	Rats	561.5±100.3	29.7±13.9	0.85±0.19	2433.3±164.7	5422.2±1162.2	0.74±0.29	0.69	74
Angoroside C	100 p.o	Rats	473.5±77.6	7.5±0.00	1.26±0.18	812.0±216.1	842.4±230.6	1.61±0.27	2.1	75

Abbreviations: ND, not detected; C_{max}, maximum concentration; Tmax, time maximum concentration; $T_{1/2}$, elimination half-life; AUC_{0-t}, area under the concentration-time curve calculated from zero up to the last measured concentration; $AUC_{0-\infty}$, area under the concentration-time curve extrapolated from zero up to infinity; MRT, mean residence time; F, bioavailability; p.o., oral administration, i.g., intragastric gavage.

Figure legends

Figure 1. Distribution of the 572 phenylethanoid glycosides in the plant kingdom.

Figure 2. The representative chemical structure of monosaccharidic PhGs, dissaccharidic PhGs, trisaccharidic PhGs, tetrasaccharidic PhGs, and pentasaccharidic PhGs (sugar moiety in red, hydroxyphenylethyl moiety in blue and hydroxycinnamic acid moiety in green).

Figure 3. A: Number of papers indexed in Web of Science related to "Phenylethanoid Glycosides" B: Times Cited of papers related to "Phenylethanoid Glycosides" by papers indexed in Web of Science. C: The number of papers published on specific phenylethanoid glycosides compound. D: The number of papers cited on specific phenylethanoid glycosides compound.

Figure 4. A summary of the potential health benefits of phenylethanoid glycosides.

Figure 5. Various phenylethanoid glycosides based products and medicines.

Figure 6. Main metabolic pathways of PhGs *in vivo* (1: hydrolysis, 2: hydroxylation, 3: sulfation, 4: glucuronidation, 5: acetylation, 6: methylation, 7: hydration, 8: deglycosylation, 9: hydrogenation, 10: dehydroxylation).

Figure 7. Different strategies to improve the bioavailability of phenylethanoid glycosides.