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Mini Review

Phenylethanoid Glycosides: A Mini Review on their Anti-liver Injury Effects and Underlying Mechanisms

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Abstract

Phenylethanoid glycosides (PhGs) are water-soluble natural compounds widely distributed in the plant kingdom, attracting significant attention from medicinal chemists due to their promising potential in pharmaceutical applications. PhGs exhibit a broad range of activities, including neuroprotective, hepatoprotective, anti-inflammatory, antioxidant, and immunomodulatory effects. This review aims to update the hepatoprotective effects of total PhG extracts and individual PhG compounds, as well as the underlying mechanisms. Additionally, we describe the structural characteristics, representative PhG compounds, and their structure–activity relationships. In brief, total PhG extracts can exert synergistic protection by reducing serum alanine aminotransferase/aspartate aminotransferase levels, suppressing oxidative stress, and attenuating inflammatory responses. Representative PhGs, including acteoside (verbascoside), echinacoside, forsythoside A (also known as forsythiaside A), and cistanoside A, protect against liver injury through modulation of the Nrf2/HO-1, NF-κB, MAPK, and TGF-β/Smad pathways, thereby regulating oxidative stress, inflammation, apoptosis, fibrosis, and lipid metabolism. Structurally, PhGs consist of a phenylethyl alcohol core, cinnamoyl residues, and glycosyl moieties. Structure–activity relationship analyses indicate that caffeoyl substitution, multiple phenolic hydroxyl groups, and optimal glycosylation patterns are key determinants of hepatoprotective efficacy.

Introduction

The liver is a vital organ essential for maintaining normal metabolic homeostasis in the body, playing a key role in the biotransformation of food, drugs, and both endogenous and exogenous substances.[1] Due to its metabolic burden and exposure to harmful chemicals, the liver is susceptible to a range of disorders, including acute and chronic inflammation, toxin- or drug-induced hepatitis, cirrhosis, and liver cancer. Primary liver injuries can ultimately lead to serious liver diseases.[2,3] It has been reported that over 10% of the global population suffers from liver-related disorders.[4] Therefore, there is an urgent need for natural products with minimal toxicity and few adverse effects to prevent and treat liver injuries.

Phenylethanoid glycosides (PhGs) are a group of natural compounds widely distributed in the plant kingdom, and most PhGs have been isolated from medicinal plants, particularly those used in traditional Chinese medicine, such as *Acanthus ilicifolius*,[5,6] *Cistanche deserticola*,[7] *Cistanche tubulosa*,[8] *Forsythia suspensa*,[9] *Plantago lanceolata*,[10] and *Callicarpa integerrima*.[11]

PhGs exhibit a broad range of pharmacological activities, including neuroprotective, hepatoprotective, anti-inflammatory, antioxidant, and immunomodulatory effects.[12] Among these, the neuroprotective effects of PhGs have been systematically documented, and several PhGs are currently being explored for the treatment of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases.[13,14] Additionally, a significant number of PhGs demonstrate hepatoprotective properties, with acteoside, a well-known PhG compound, currently undergoing phase II clinical trials for the treatment of acute hepatitis.[15]

In our previous studies, the total PhGs from *A. ilicifolius* showed promising hepatoprotective effects against carbon tetrachloride-induced hepatotoxicity, and PhG compounds, namely acteoside and isoacteoside, were regarded as the key hepatoprotective substances in *A. ilicifolius*.[5,6,16] Moreover, a pharmacokinetic study of four

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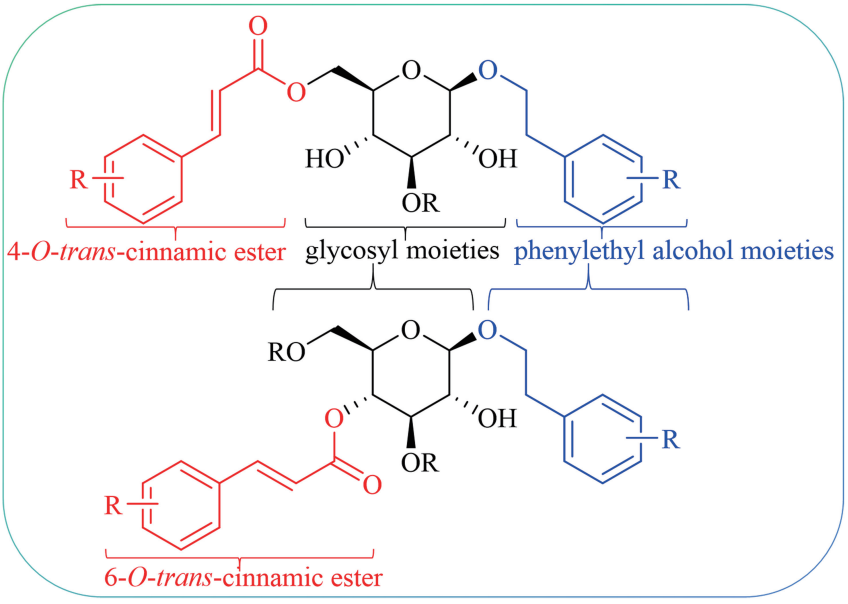

Fig. 1. Basic chemical structure of phenylethanoid glycosides.

PhGs (acteoside, isoacteoside, martynoside, and crenatoside) from *A. ilicifolius* in rat plasma showed that they all exhibited double peaks on concentration–time curves (at about 0.5 h and 6 h), and their elimination half-lives ($t_{1/2}$) were different, ranging from 3.42 h to 8.99 h.[17] In addition, we proved that the traditional Chinese medicine formula Le-Cao-Shi, containing *A. ilicifolius* as one main single herb, had anti-liver injury effects, and the underlying mechanisms mainly concerned anti-inflammatory and antioxidant pathways.[2,18–20]

To date, no systematic review has been published on the anti-liver injury effects of PhGs. Herein, we present a focused review of the literature on the basic chemical structure of PhGs and the anti-liver injury activities of total PhG extracts and individual PhG compounds.

Basic chemical structure and typical compounds of PhGs

PhGs are cinnamic acid–containing sugar compounds, forming a unique class of carbohydrate molecules of plant origin that have received considerable attention in medicinal chemistry.[21] In general, most PhGs are composed of three groups: phenylethyl alcohol moieties, cinnamic acid residues (e.g., caffeic acid), and glycosyl moieties (glucose as a central unit) (Fig. 1). The phenylethyl alcohol group is attached to the anomeric carbon of glucose in *β*-configuration. The cinnamic acid group usually exists in trans stereochemistry and is placed at the 4th- or 6th-hydroxyl group of the glucose ring (Fig. 1).[21] PhGs typically include mono-, di-, tri-, and tetraglycosides, with triglycosides being the most common form.[22,23] It is believed that the glycosides serve as a storage form of phenols, which are easily stored in plants and do not interfere with essential cellular processes.[22] In addition, intramolecular acyl migration and cis-/trans configurational changes of acyl and glycosyl groups commonly occur in this chemical class. These structural properties make PhGs susceptible to oxidation and degradation. As a result, they are vulnerable to factors such as light, temperature, and pH.[24]

The earliest references to PhGs in the literature involve the isolation of echinacoside (Fig. 2), a triglycosidic phenylethanoid extracted from *Echinacea angustifolia* (Asteraceae) in 1950, with its structure determined in 1983. Verbascoside, first isolated in 1963, was structurally characterized in 1968 and again isolated in 1966, but was then named acteoside (Fig. 2). There has been considerable confusion in the literature regarding its name, although acteoside is now the widely accepted term for this natural product.[22] Acteoside, which contains a hydroxysalidroside residue linked to caffeoyl and rhamnose moieties, has been the most extensively studied and documented PhG due to its potential health benefits in humans.[25] Biosynthetic studies of acteoside have shown that the phenylpropanoid moiety is derived from the amino acid phenylalanine or cinnamic acid, while the hydroxyphenylethanol portion originates from tyrosine or tyramine.[22]

Salidroside is the most extensively studied PhG, with over 1,770 publications.[24] It is a monoglycosidic PhG consisting of phenylethanol and glucose (Fig. 2). Due to its relatively simple structure, salidroside exhibits significantly higher oral bioavailability (51.97%) compared to other PhGs.[26] Salidroside has demonstrated a range of activities, such as hepatoprotective, antioxidant, neuroprotective and anticancer effects.[27]

Forsythoside A is a structurally unique macrocyclic PhG featuring a 15-membered ring (Fig. 2). It was first isolated from *F. suspensa* and exhibited significant neuroprotective activities,[9] along with an unexpected solvent-dependent conformational transformation.[28]

Anti-liver injury activities of PhGs

Total PhG extracts

Total PhGs from *A. ilicifolius* L. could decrease alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in CCl_4-induced mice. In addition, they enhanced superoxide dismutase activity and decreased malondialdehyde (MDA) levels in both serum and liver tissues. Moreover, total PhGs markedly downregulated the *in vivo* protein expression of TNF-α and IL-1β.[6]

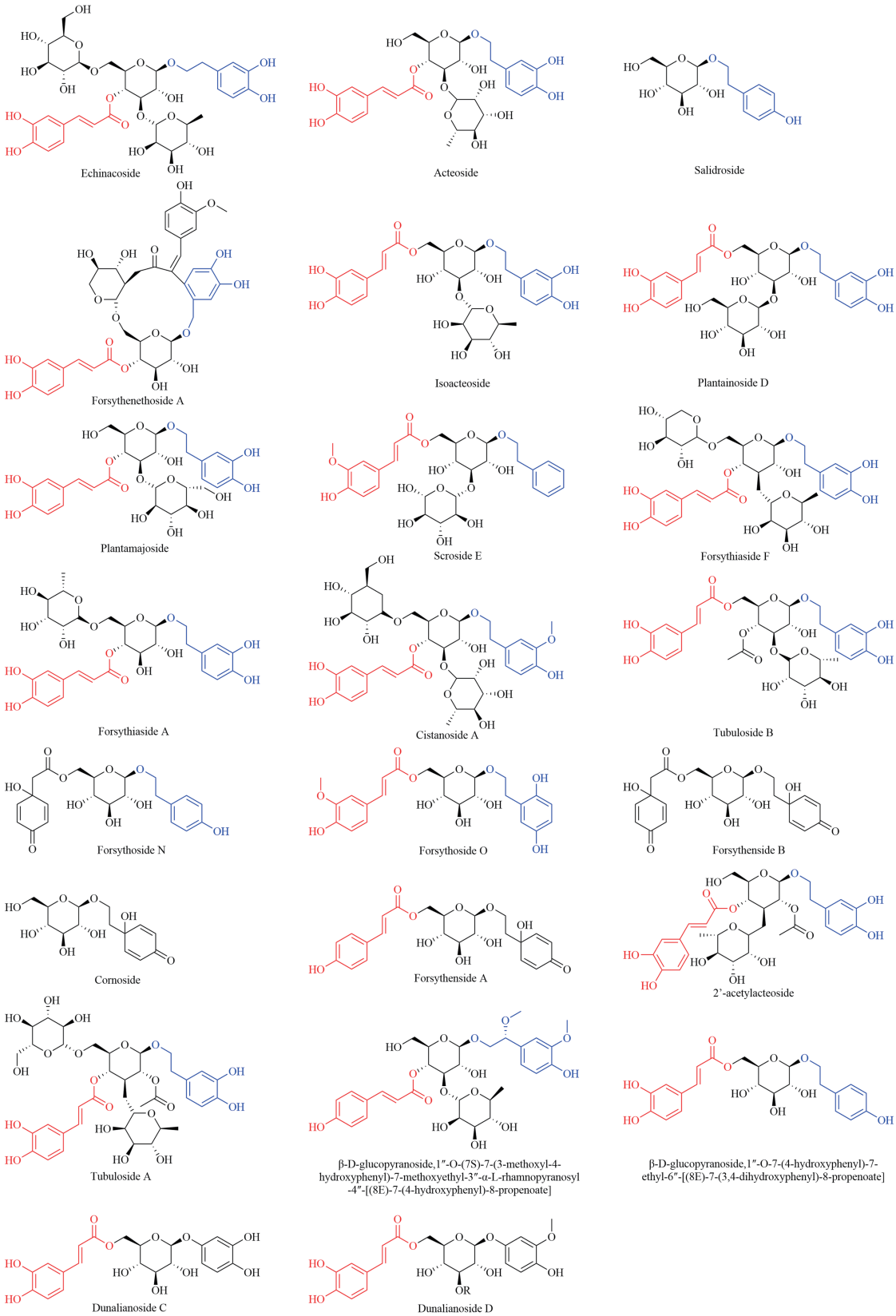

Fig. 2. Representative chemical structures of phenylethanoid glycosides.

Total PhGs from *C. tubulosa* exhibited significant anti-fibrotic effects against liver injury, potentially through the inhibition of TGF-β1/Smad signaling activation.[29] Yuan *et al*.[30] further reported that total PhGs from *C. tubulosa* could suppress the growth of H22 hepatocellular carcinoma cells both *in vitro* and *in vivo*, and induce apoptosis via both extrinsic and intrinsic apoptosis pathways. Subsequently, they demonstrated that total PhGs could significantly inhibit the growth of HepG2 and BEL-7404 cells through the induction of cell cycle arrest and apoptosis. These effects were associated with the activation of MAPK signaling, as evidenced by increased phosphorylation of p38, JNK, and ERK1/2, as well as a mitochondria-dependent apoptotic pathway characterized by a reduction in mitochondrial membrane potential.[8]

Acteoside and its isomer isoacteoside

According to ongoing clinical trials registered on the International Clinical Trials Registry Platform (http://apps.who.int/trialsearch), a comparative evaluation of acteoside and silymarin as hepatoprotective agents in patients with acute hepatitis has been conducted.[24]

The hepatoprotective activities of PhGs isolated from *A. ilicifolius* have also been investigated. Zhang *et al*.[17] reported that acteoside could significantly reduce ALT and AST levels in a CCl_4-induced mouse model, exhibiting superior hepatoprotective efficacy compared with the positive control silybinin. In contrast, its isomer isoacteoside displayed markedly weaker hepatoprotective activity, although it was still able to partially decrease ALT and AST levels.[17] Isoacteoside isolated from the desert plant *C. tubulosa* could inhibit *D*-galactosamine (*D*-GalN)-induced hepatocyte death and also exhibited *in vivo* hepatoprotective effects at doses ranging from 25 to 100 mg/kg, po.[31]

The defatted aqueous methanolic extract of *Plantago major* exhibited notable hepatoprotective and antioxidant effects in rats, with efficacy comparable to that of the commercially used drug silymarin. Acteoside was identified as the major constituent of the extract. *In vitro* studies further demonstrated that acteoside inhibited lipopolysaccharide (LPS)-induced nitric oxide production in RAW264.7 macrophages (IC_{50}, 75.0 μM) and effectively scavenged superoxide radicals (IC_{50}, 1.51 μM) and DPPH radicals (IC_{50}, 11.27 μM).[32]

Lee *et al*.[33] demonstrated that acteoside exerted potent hepatoprotective effects against CCl_4-induced hepatic injury in mice. Acteoside dose-dependently reduced serum ALT and AST levels, suppressed hepatic MDA formation, and prevented the depletion of reduced glutathione in liver tissues. The hepatoprotective effects of acteoside may be attributed to its ability to block the bioactivation of CCl_4 by inhibiting CYP2E1 activity and protein levels.[33] Acteoside isolated from *Houttuynia cordata* Thunb. exhibited comparable hepatoprotective activity against *D*-GalN–induced WB-F344 cell damage, similar to bicyclol, at a concentration of 10 μM.[34] Acteoside isolated from *Cirsium setosum* was also reported to exhibit moderate hepatoprotective activities against *D*-GalN–induced HL-7702 cell damage at a concentration of 10 μM.[35] Moreover, acteoside could effectively inhibit the pathological progression of alcoholic hepatitis by significantly attenuating NF-κB signaling activation in HepG2 cells.[36] In addition, its effects on lipid accumulation in HepG2 cells have been investigated. RNA-sequencing analyses revealed that acteoside could ameliorate lipid accumulation by regulating glycolysis, AMP-activated protein kinase signaling, and fatty acid degradation pathways.[37] Acteoside isolated from *C. tubulosa* exhibited significant anti-liver fibrotic effects, potentially through the inhibition of TGF-β1/Smad signaling.[29]

In immunological liver injury models, acteoside administered orally at doses of 50, 150, and 300 mg/kg effectively attenuated BCG/LPS-induced liver injury in mice, as evidenced by reductions in the elevated liver index, serum AST and ALT levels, and hepatic NO and MDA contents. In parallel, acteoside restored hepatic superoxide dismutase activity and markedly alleviated the overall degree of liver injury.[38] Xiong *et al*.[39] showed the inhibitory effect of acteoside on apoptosis in *D*-GalN and LPS-induced liver injury. Moreover, acteoside isolated from *C. tubulosa* has been shown to inhibit *D*-GalN-induced hepatocyte death and to exhibit *in vivo* hepatoprotective effects at doses ranging from 25 to 100 mg/kg, po.[31] Ma *et al*.[40] found that acteoside could upregulate p53 protein and abrogate kallikrein-related peptidase expression, ultimately decreasing angiogenesis in hepatocellular carcinoma at concentrations of 350 and 700 μM. Acteoside showed chemopreventive potential against dietary carcinogen diethylnitrosamine-induced rat hepatocarcinogenesis through regulating STAT3-mediated oxidative stress and apoptosis.[41]

Cui *et al*.[42] found that metabolites in rat urine after the administration of acteoside, such as hydroxytyrosol, 3-hydroxyphenylpropionic acid, and caffeic acid, exhibited higher hepatoprotective activities by regulating oxidative stress, lipid peroxidation, and inflammatory responses in a GalN/LPS-induced acute hepatic injury mouse model than native acteoside. It was proposed that acteoside metabolites in rat urine could be responsible for its potent hepatoprotective activity as well as other therapeutic effects.[42]

Other individual PhGs isolated from medicinal plants

Echinacoside

Echinacoside isolated from *C. tubulosa* showed anti-liver fibrotic effects, potentially by inhibiting TGF-β1/Smad signaling.[29] It could attenuate diethylnitrosamine-induced HCC in mice, exerting antiproliferative and proapoptotic effects on the HepG2 hepatocellular carcinoma cell line by decreasing TREM2 expression and modulating PI3K/AKT signaling.[43] Furthermore, echinacoside ameliorated D-GalN- and LPS-induced acute liver injury in mice by inhibiting apoptosis and inflammation, characterized by substantial inhibition of hepatocyte apoptosis and significant reduction in inflammatory markers, including myeloperoxidase, extracellular nucleosomes, high-mobility group box 1, and inflammatory cytokines in the plasma.[44] It could also inhibit *D*-GalN–induced hepatocyte death and exhibit *in vivo* hepatoprotective effects at doses ranging from 25 to 100 mg/kg, po.[31] Additionally, echinacoside could provide a protective effect against acute hepatic injury induced by CCl_4 in rats, primarily through its antioxidative activity.[45]

Forsythoside A and F

Forsythoside F (Fig. 2), isolated from *H. cordata*, exhibited comparable hepatoprotective activity against *D*-GalN–induced WB-F344 cell damage, similar to bicyclol at a concentration of 10 μM, while forsythoside A (Fig. 2) showed weaker hepatoprotective effects.[34] However, forsythoside A was found to mitigate GalN/LPS-induced liver injury by inhibiting NF-κB and Nrf2 activation.[46] The variations in anti-liver injury activity of forsythoside A may be attributed to differences in inducers used and pharmacological models employed.

Cistanoside A

Luo *et al*.[47] reported that cistanoside A (Fig. 2), isolated from *C. deserticola*, exhibited protective effects against CCl_4-induced

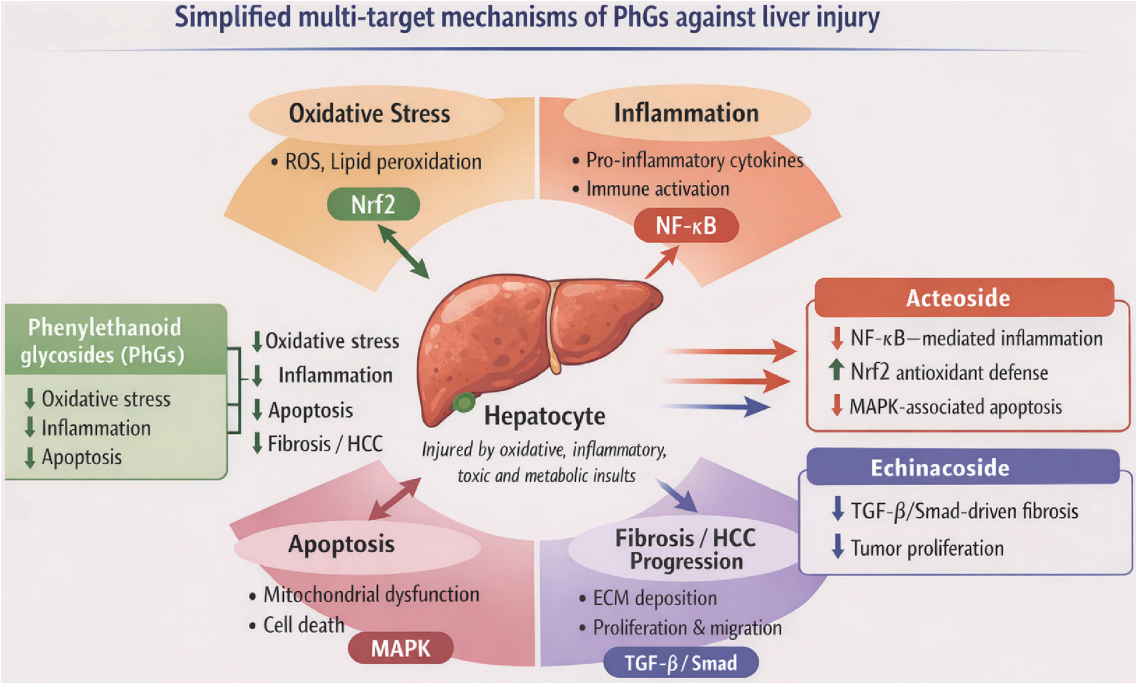

Fig. 3. Multi-target mechanism of PhGs against liver injury. ECM, extracellular matrix; HCC, hepatocellular carcinoma; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-B; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TGF-β, transforming growth factor-β.

hepatotoxicity in mice. The mechanism of action involved increased free radical clearance, alleviation of lipid peroxidation damage, and improvement of mitochondrial respiratory chain function.[47] Additionally, cistanoside A showed protective effects against alcohol-induced hepatotoxicity in mice by improving hepatic function, reducing steatosis and inflammatory infiltration, enhancing free radical clearance, alleviating lipid peroxidation, and restoring mitochondrial energy metabolism.[48] Further studies by Luo *et al*.[49] on ethanol-induced damage in primary cultured mouse hepatocytes revealed that cistanoside A could enhance cell survival, reduce apoptosis and necrosis, and promote the expression of the anti-apoptotic factor Bcl-2 while inhibiting the expression of the immediate early gene c-Fos.

Tubuloside A and B

Tubuloside A, isolated from *C. tubulosa*, has been shown to inhibit *D*-GalN–induced hepatocyte death.[31] Moreover, Tureyen *et al*.[50] found that tubuloside A could alleviate nonsteroidal anti-inflammatory drug-induced hepatorenal oxidative injury via the Nrf2/HO-1 pathway, involving changes in the mRNA expression of genes Nrf2, HO-1, NQO1, IL-6, iNOS, COX-2, TNF-α, IL-1β, and NF-κB, as well as apoptotic processes (Bcl-2, caspase-3, and Bax). Tubuloside B, isolated from *C. deserticola,* shows strong potential in inhibiting the migration of hepatocellular carcinoma. Its effect is attributed to modulation of the Hippo-YAP pathway.[7]

Forsythoside A, N, and O

Recent evidence further supports the hepatoprotective potential of PhGs in metabolic liver disease. Forsythoside A, identified from *F. suspensa* fruits, significantly alleviated metabolic dysfunction–associated fatty liver disease by reducing hepatic steatosis, inflammation, and liver injury both *in vitro* and *in vivo*. Mechanistically, forsythoside A exerted its protective effects through metabolic remodeling, restoration of lipid homeostasis, and suppression of inflammatory responses, particularly via regulation of the IL-17/MAPK signaling pathway, highlighting PhGs as promising multi-target agents for metabolic liver disorders.[51] Two PhGs, forsythoside N and forsythoside O, isolated from the fruits of *F. suspensa*, exhibited strong hepatoprotective activities against *N*-acetyl-*p*-aminophenol-induced HepG2 cell damage.[9]

Others

PhGs such as plantainoside D, plantamajoside, and scroside E, isolated from *H. cordata*, exhibited comparable hepatoprotective activity against *D*-GalN–induced WB-F344 cell damage.[34] Forsythenside A, forsythenside B, and cornoside, isolated from the fruits of *F. suspensa*, exhibited strong hepatoprotective activities against *N*-acetyl-*p*-aminophenol-induced HepG2 cell damage.[9] Compound 2′-acetylacteoside, isolated from *C. tubulosa*, has been shown to inhibit *D*-GalN–induced hepatocyte death.[31] *β*-*D*-glucopyranoside, 1″-*O*-(7*S*)-7-(3-methoxyl-4-hydroxyphenyl)-7-methoxyethyl-3″-α-*L*-rhamnopyranosyl-4″-[(8*E*)-7-(4-hydroxyphenyl)-8-propenoate], *β*-*D*-glucopyranoside, 1″-*O*-7-(4-hydroxyphenyl)-7-ethyl-6″-[(8*E*)-7-(3,4-dihydroxyphenyl)-8-propenoate], dunalianoside C, and dunalianoside D, isolated from *C. setosum*, exhibited moderate hepatoprotective activities against *D*-GalN–induced HL-7702 cell damage at a concentration of 10 μM.[35]

To provide a more comprehensive understanding of the multi-target mechanisms by which PhGs protect the liver, we have created a diagram (Fig. 3) illustrating how different PhGs, such as acteoside and echinacoside, target various pathways involved in liver injury. This diagram integrates key pathological processes such as oxidative stress, inflammation, apoptosis, and fibrosis, showing how these pathways interact within hepatocytes. The diagram focuses on four main pathological processes: oxidative stress, inflammation, apoptosis, and fibrosis, with each pro-

cess linked to the major signaling pathways (e.g., Nrf2, NF-κB, MAPK, TGF-β) that PhGs influence. PhGs such as acteoside and echinacoside have been shown to modulate these pathways in different ways.

Structure-activity relationships of PhGs

Some studies have reported that the anti-liver injury effect of PhG compounds is largely attributed to the caffeoyl residue in the molecule.[52] Others have suggested that the phenylethyl moiety also plays a critical role, as the radical scavenging activity of PhGs may arise from aromatic hydroxyl groups present not only in the caffeoyl group but also in the phenylethyl moiety.[39] A recent study revealed that the structure-activity relationship of phenylethanoids in protecting against *D*-GalN–induced cytotoxicity in mouse primary hepatocytes is as follows: (1) compounds with a caffeoyl group exhibited stronger activity than those with a feruloyl group; (2) PhGs with a disaccharide glycosyl moiety showed stronger activity than those with a monosaccharide or trisaccharide.[53] Specifically, acteoside, a PhG compound that combines 4,5-dihydroxyphenylethanol through ester bonds and glycosidic bonds with C3-linked rhamnose C1-position-D-glucopyranoside, is a natural and water-soluble phenylpropanoid glycoside and can penetrate the blood-brain barrier.[54]

Limitations

While this review provides a comprehensive overview of the anti-hepatotoxic effects of PhGs, several limitations should be considered. First, the majority of the studies discussed are preclinical, and clinical data supporting the hepatoprotective potential of PhGs are limited. Thus, the translation of these findings to human settings remains to be fully established. Additionally, the experimental models, dosing regimens, and methodologies used in the studies vary significantly, which can complicate direct comparisons and may influence the interpretation of results. Furthermore, while the mechanisms of action of PhGs are explored, the available data on *in vivo* targets and the pharmacokinetic–pharmacodynamic relationships of these compounds are still limited. Future studies should focus on clinical trials and a more in-depth investigation of pharmacokinetics, target validation, and structure–activity relationships to confirm the therapeutic potential of PhGs for liver diseases.

Conclusions

A large number of PhG extracts and compounds from various herbs have demonstrated promising anti-liver injury effects. PhGs are gaining significant attention due to their structural diversity and potential pharmacological activities. PhGs show significant hepatoprotective potential through their multi-target mechanisms, addressing critical processes such as oxidative stress, inflammation, apoptosis, and fibrosis. However, challenges remain in optimizing their therapeutic use, particularly due to low oral bioavailability and the complexity of their metabolic pathways. Future research should focus on designing PhG derivatives that combine enhanced pharmacological activity with improved bioavailability, potentially by modifying glycosylation patterns or exploring acylation strategies. Additionally, systematic studies on the *in vivo* action networks of PhG metabolites, such as hydroxytyrosol from acteoside, are crucial to understand how these metabolites contribute to liver protection. The application of computational chemistry and artificial intelligence could facilitate the design of PhGs with enhanced specificity for key liver injury-related pathways, such as TGF-β and Nrf2. Moreover, exploring the role of gut microbiota in the metabolism of PhGs may open new avenues for improving their therapeutic efficacy. Addressing these areas will help optimize the use of PhGs in liver injury treatment and guide the development of more effective PhG-based therapies.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Writing–original draft (QZ), investigation (QZ, HF, YPH, RG, SJY, CYW), data curation (QZ, HF), methodology (YPH), conceptualization (RG), formal analysis (SJY), writing–review & editing (SJY, CYW), and supervision (CYW). All authors have approved the final version and publication of the manuscript.

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