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Review Article

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The Hepatoprotective Effects of Natural Products Against Acetaminophen *via* Involvement of Nrf2-ARE Signaling Pathway: A Systematic Review

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Abstract

Acetaminophen (APAP) is a well-recognized analgesic and an antipyretic compound. It is the prevalent reason for Acute Liver Failure (ALF) in numerous countries. The generation of a by-product including the N-acetyl-*p*-benzoquinone imine (NAPQI) is implicated in APAP hepatotoxicity which cannot be completely detoxicated at high doses. N-acetylcysteine (NAC) is the major treatment for APAP overdose. However, it causes side effects including vomiting and even shock in some individuals. Numerous studies have revealed that Natural Products (NPs) can help alleviate APAP-induced liver toxicity. Activation of nuclear factor erythroid 2-related factor 2 (Nrf2)/Antioxidant Response Element (ARE) signaling pathways is regarded as one of the mechanisms of the NPs as protective agents. Nrf2 enhances the production of cytoprotective enzymes such as SOD, NQO1, and HO-1. Therefore, the proposed function of the Nrf2-ARE signaling pathway as a defense mechanism of NPs against liver injury induced by APAP is reviewed.

Keywords: Acetaminophen, Acetylcysteine, Antioxidant, Antipyretics, Liver failure, Protective agents

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Introduction

Acetaminophen (APAP) is an eminent analgesic and an antipyretic drug (1). In therapeutic doses, APAP is safe and primarily converts into inactive metabolites through the glucuronidation and sulfation pathways. A small amount is also converted by cytochrome P450 enzymes into noxious metabolite N-acetyl-*p*-benzoquinone imine (NAPQI). This electrophilic compound quickly binds to Glutathione (GSH), a sulfhydryl donor, and eventually detoxified (2). However, in toxic doses, high levels of NAPQI are produced. Depletion of intracellular GSH resources along with extreme production of NAPQI, creates Reactive Oxygen Species (ROS) which causes hepatocyte death, extensive hepatic necrosis, and even fulminant liver failure (3). Excessive intracellular ROS triggers the activation of c-Jun N-terminal Kinases (JNK), enhancing both the phosphorylation and migration of JNK into the mitochondria.

Thus, it further increases mitochondrial oxidative stress and triggers the mitochondrial permeability transition, leading to hepatocyte necrosis. Activated JNK strengthens hepatic injuries by altering redox status, regulating the activity of the Bcl-2 protein family, and triggering mitochondrial dysfunction. Oxidative stress and JNK activation are considered as important mediators in liver damage caused by APAP (4,5). The liver is a crucial organ in the human body and has important functions including detoxification, biotransformation, plasma protein synthesis, and glycogen storage (5). In fact, APAP-induced liver damage is the primary reason for Acute Liver Failure (ALF) in a large number of countries and accepted abundant attention in the clinical (6). APAP overdoses are the primary cause of ALF in the U.S., accounting for 50% of all ALF cases and associated with a 30% mortality rate (7).

N-acetylcysteine (NAC) is primary therapy for APAP overdose. However, it only works for a short period of time and is not always beneficial for patients. Moreover, it has been observed that NAC causes side effects including vomiting and even shock in some individuals (8-10). On the other side, Natural Products (NPs) have been used to prevent and treat many diseases. They have low cost and good efficacy. Numerous researches have been confirmed that NPs with active compounds can diminish liver damage caused by APAP (11,12). NPs are able to reduce centrilobular necrosis, liver enzymes, pro-inflammatory cytokines and enhance GSH, CAT and HO-1. The activation of Nuclear factor E2-related factor 2 (Nrf2) is the main way NPs demonstrate their detoxifying effects against liver injury caused by APAP (11,12). Nrf2 is an essential cellular redox sensor that controls antioxidant processes and related target genes. Kelch ECH associating protein 1 (Keapl) is an inhibitor of Nrf2 that typically keeps Nrf2 in the cytoplasm. Nrf2 is released from Keap 1 and transported to the nucleus in response to a stimulus or medication.

There, it binds to Antioxidant Response Elements (AREs) and increases the expression of genes involved in antioxidant activity and detoxification, including heme oxygenase-1 (HO-1), glutamate cysteine ligase catalytic/modifier (GCLC/GCLM) subunit, Superoxide Dismutase (SOD), and NAD (P)H: quinone oxidoreductase (13). It has been demonstrated that Nrf2 guards the liver against several xenobiotics through transcriptional up-regulation of antioxidant enzymes and activation of the Keap1-Nrf2 pathway. While many reviews have addressed the liver-protective properties of natural products, this paper specifically examines their mechanistic interactions with the Nrf2-ARE signaling pathway in acetaminophen-induced liver damage (Figure 1). By systematically integrating preclinical data, molecular mechanisms, and chemical classifications, this review provides a consolidated framework for identifying lead compounds that could be developed into safer therapeutic candidates compared to conventional treatments such as N-acetylcysteine.

Search strategy

Scopus, PubMed, and Web of Science were searched. Search strategy was presented in table 1. Review articles were excluded, and only pertinent *in vitro* and *in vivo* studies were chosen. The authors found 766 articles in the online databases, from which duplicates (416), irrelevant articles (297), and those in non-English (2) were excluded. The other 51 articles were thoroughly reviewed and incorporated into this review (Figure 2). No human studies had been reported yet.

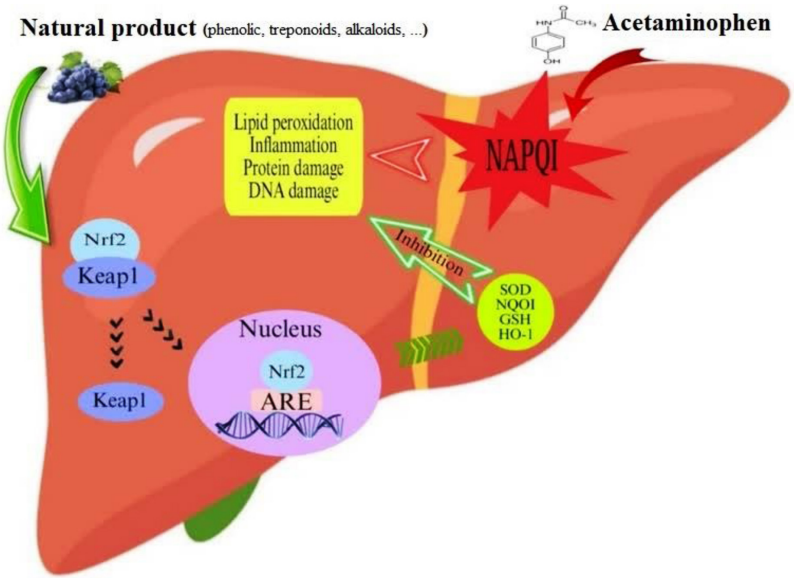


Figure 1. The toxic effect of acetaminophen in the liver and protective mechanisms of NPs though Nrf-ARE signaling pathway.

Table 1. Search strategy of relevant studies on protective effects of natural products against acetaminophen (APAP) hepatotoxicity

Database	Search strategy	Results
PubMed	("GA-Binding Protein Transcription Factor"[mesh] OR nrf2 OR "GA Binding Protein Transcription Factor" OR "Nuclear Respiratory Factor-2" OR "Nuclear Respiratory Factor 2" OR "GA-Binding Protein" OR "GA Binding Protein" OR "GABP Transcription Factor" OR "nuclear factor erythroid 2 (NFE2)-related factor 2") AND (Acetaminophen[mesh] OR Acetominophen OR Hydroxyacetanilide OR APAP OR p-Acetamidophenol OR p-Hydroxyacetanilide OR Paracetamol OR N-(4-Hydroxyphenyl)acetanilide OR Tylenol OR Anacin-3 OR Anacin 3 OR Anacin3 OR Datril OR Panadol OR Acamol OR Algotropyl) AND (Hepatotoxicity OR liver* OR Liver[mesh])	302
Scopus	TITLE-ABS-KEY((nrf2 OR "GA Binding Protein Transcription Factor" OR "Nuclear Respiratory Factor-2" OR "Nuclear Respiratory Factor 2" OR "GA-Binding Protein" OR "GA Binding Protein" OR "GABP Transcription Factor" OR "nuclear factor erythroid 2 (NFE2)-related factor 2") AND (Acetominophen OR Hydroxyacetanilide OR APAP OR p-Acetamidophenol OR p-Hydroxyacetanilide OR Paracetamol OR N-(4-Hydroxyphenyl)acetanilide OR Tylenol OR Anacin-3 OR Anacin 3 OR Anacin3 OR Datril OR Panadol OR Acamol OR Algotropyl) AND (Hepatotoxicity OR liver*))	173
WoS	TS=((nrf2 OR "GA Binding Protein Transcription Factor" OR "Nuclear Respiratory Factor-2" OR "Nuclear Respiratory Factor 2" OR "GA-Binding Protein" OR "GA Binding Protein" OR "GABP Transcription Factor" OR "nuclear factor erythroid 2 (NFE2)-related factor 2") AND (Acetominophen OR Hydroxyacetanilide OR APAP OR p-Acetamidophenol OR p-Hydroxyacetanilide OR Paracetamol OR N-(4-Hydroxyphenyl)acetanilide OR Tylenol OR Anacin-3 OR Anacin 3 OR Anacin3 OR Datril OR Panadol OR Acamol OR Algotropyl) AND (Hepatotoxicity OR liver*))	285

Natural products against acetaminophen-induced hepatotoxicity

Herein, we report the usage of numerous natural products as a strategy against acetaminophen-induced hepatotoxicity.

Phenolic compounds

Phenolic compounds feature an aromatic ring that includes one or several hydroxyl groups, encompassing various classes of compounds such as phenolic acids, flavonoids, lignans, tannins, quinones,

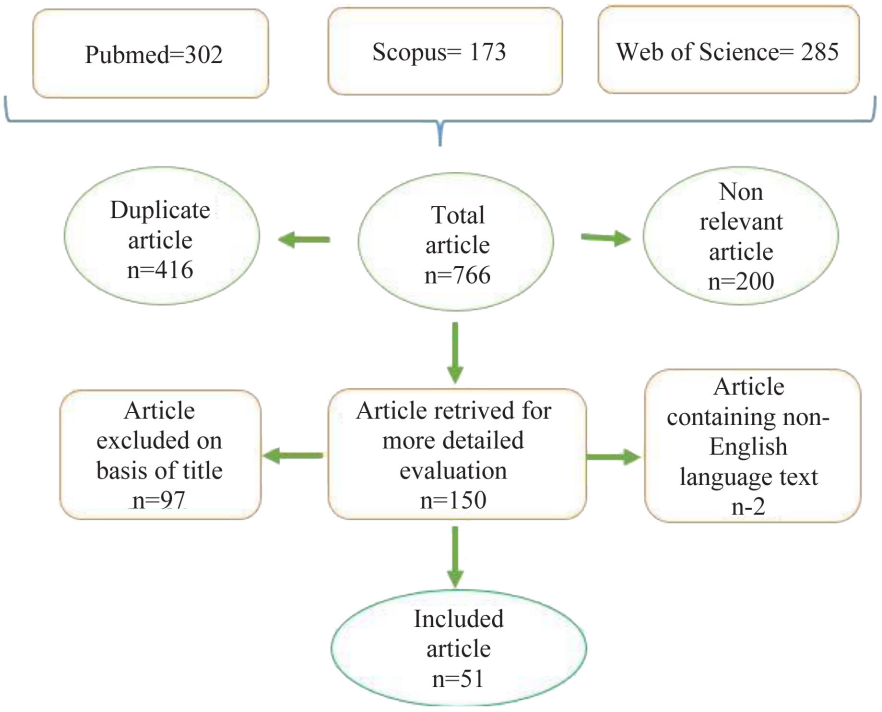


Figure 2. Flow diagram of narrative literature search representing the included and excluded studies.

etc. (14). They have protective effect on liver against toxic effects of chemical compounds (15,16).

Urolithin A (UA, 1), a naturally occurring phenolic compound, is produced from ellagitannins and ellagic acid in the gut microflora. UA displays a variety of biological functions, including anti-inflammatory, anticancer, and renal protective effects (17). The therapeutic impact of UA was examined in acute liver injury caused by APAP. It was observed that UA is better than NAC concerning dosage and therapeutical time window. Transcriptomics assay explored that UA increased mitophagy and activated Nrf2/ARE signaling pathway in the liver. As a result, the level of protective enzymes including HO-1 and NQO1 were enhanced (18).

Rosmarinic acid (RA, 2) a natural polyphenol found in various aromatic plants, exhibits numerous pharmacological properties, including antiviral, antidiabetic, anti-inflammatory, and anticancer effects (19). A previous study showed that RA has protective effect on APAP-induced hepatotoxicity in mice (20). The results demonstrated that RA diminished the serum ALT and AST levels, ameliorated the histological injury, and reduced generation of IL-1β and IL-18 in the liver tissue. Pre-treatment with RA could inhibit apoptosis and increased the cell viability and migration ability in APAP-received HepG2 cells. From the mechanistical point of view, it has a protective role against APAP hepatotoxicity via activation of Nrf2 and suppression of the NIMA-related kinase 7 (NEK7) -NLRP3 pathway (20).

Gastrodin (GL, 3) is a key active phenolic glycoside isolated from *Gastrodia elata* (21). GL has a comprehensive range of effects, such as anti-migraine, antioxidant, and anti-inflammation (22). In 2022, the hepatoprotective effect and mechanism of GL on APAP-induced liver injury was evaluated (23). The results indicated that GL diminished the levels of TNF-α, IL-1β, IL-6, ALT and AST in serum. Also, this polyphenol decreased hepatic MDA content and increased SOD activity. In addition, GL inhibited ERK/JNK/MAPK signaling pathway but promoted Nrf2 level (23).

Sinapic acid (SA, 4) is a phenolic compound that mainly presented in grains, vegetables, and berries (24). This compound has antioxidant, anti-inflammatory and hepatoprotective activities. In a study, the hepatoprotective effect of SA in APAP-induced liver toxicity in male C57BL/6 mice was investigated. SA decreased the levels of ALT, AST and ALP and improved the activity of Sirt-1, HO-1, Nrf2, and SOD. It was observed that the protective

role of SA is mediated with NF-κB/Nrf2/HO-1 signaling pathway. Also, SA up-regulated Sirt-1 and enhanced mitochondrial integrity and lysosomal stabilization (25).

Chlorogenic acid (CGA, 5), a biologically active phenolic acid, is playing several therapeutic roles such as antipyretic, anti-inflammatory, anti-obesity and neuroprotective effects (26). The alleviative effect of CGA on APAP-induced liver damage was revealed in mice (27). Results showed that CGA presented hepatoprotective effect by activating Nrf2 signaling pathway *via* blocking the binding of Nrf2 to its inhibitor protein Keap1. Regulation of Nrf2 with CGA enhanced the level of NQO1 and HO-1 in hepatocytes. Results of other studies exhibited that CGA reduced the contents of High Mobility Group Box 1 (HMGB1) and Heat Shock Protein 60 (HSP60) in mice. Also, this phenolic compound improved the increased hepatic infiltration of immune cells. Nrf2 is necessary for regulating the mitochondrial HSP60 release (28).

Guavinoside B (GUB, 6) is the major active constituents synthesized in fruits of *Psidium guajava* (29). The protective effect of this compound was investigated against APAP-induced liver damage (4). GUB markedly improved the levels of ALT, AST, SOD, ROS and TNF-α in C57BL/6 mice. Also, hepatocyte infiltration and necrosis were alleviated in intoxicated animals. *In vitro* test revealed that GUB alleviated APAP-induced liver injury by activating Nrf2 signaling pathway and inhibiting JNK signaling pathway.

Honokiol (HO, **7**), as a lignan, is the main component of the Chinese medicinal *Mannolia officinalis* (12). This active compound has antitumor, anti-thrombosis, and anti-inflammatory effects (30). HO presented ameliorative effect against APAP-induced liver damage in mice. By induction of inhibition of CYP2E1 and CYP2A1, HO could reduce APAP-protein adducts. APAP-protein adducts are generated by interaction of NAPQI with sulfhydryl groups on cysteine residues of hepatocellular proteins. HO induces activations of Nrf2 and its target enzymes, such as Glutathione Synthetase (GS) and Glutathione S-Transferase (GST) (12).

Tovophyllin A (TA, 8) is an active component extracted from *Garcinia mangostana* pericarps. It has antioxidant, anti-inflammatory and neuroprotective activities (3). The protective activity of TA against APAP-induced hepatic damage was investigated (3). It was demonstrated that TA pretreatment markedly decreased abnormal elevation of ALT, AST, LDH and ALP. In a dose dependent manner, TA reduced the extent and severity of the hepatic lesions. TA activated Nrf2 signaling pathway and enhanced the levels of its downstream enzymes including NQO1, HO-1 and GCLC/GCLM (3).

Corilagin (COL, 9), a hydrolyzable gallotannin, is one of the active ingredients of medicinal plant such as *Phyllanthus amarus* and *Geranium carolinianum*. It has antitumor, antioxidant and anti-inflammatory properties (31). The protective role of COL on APAP-induced liver damage was investigated. It was observed that COL reduced mortality and AST and ALT levels, as well as histopathological liver changes in mice. Keap1-Nrf2-ARE, an important antioxidant signaling pathway was activated by COL in in HepG2 cells. Moreover, this ellagitannin activated the AMPK/GSK3β signaling pathway in HepG2 cells (32).

Salvianolic acid C (SAC, 10) is a water-soluble active component that presented in the roots of *Salvia miltiorrhiza*. This herbal compound comprised of a single unit of caffeic acid and two units of tashinol (33). SAC is used in the treatment of cardiovascular diseases and cancer cell apoptosis. SAC controlled the enhancement of Total Bilirubin (T-Bil), Total Cholesterol (TC), and Triacylglycerol (TG) in APAP-received animals (33). This organic antioxidant increased the levels of GSH, SOD, Gpx. SAC was able to activates Keap1/Nrf2/ HO-1 pathway and reduced mitochondrial oxidative stress and inflammatory response (33).

Caffeic acid (CA, 11) is a type of phenolic acid found in coffee, certain fruits, and herbs (34). CA exhibits various pharmacological effects such as anti-inflammatory, anticancer, and antioxidant properties (34). Pang and co-workers showed that CA can prevent APAP-induced liver injury in mice. CA could diminish the level of liver enzymes and ROS. They revealed that CA enhanced the activation of Nrf2 by reducing Keap1 expression and inhibiting the binding of Keap1 to Nrf2 (35).

Salvianolic acid B (Sal B, 12) is a primary active

compound found in *Salvia miltiorrhiza*. Recent studies have shown that Sal B possesses anti-aging, cardioprotective, anti-fibrotic and anti-inflammatory properties (36). Lin and his-colleagues showed that this phenolic compound had ameliorative property on APAP hepatotoxicity (37). They observed that Sal B can enhance the levels of phase II detoxification enzymes by induction of Nrf2. Their findings exhibited that Sal B enhanced Nrf2, HO-1 and GCLC levels via activation of the PI3K and protein kinase C (PKC) pathways.

Flavonoids have the general structure of a 15-carbon skeleton, comprised from two benzene rings which connected through a pyran ring (38). They are a group of NPs that synthesized in fruits, vegetables, grains, flowers, and tea. These compounds have protective effects on liver injury caused by various factors (39,40). Pectolinarigenin (PNG, 13) is an active flavonoid presented in various plants such as *Aegiphila integrifolia* and *Chromolaena odorata.* It has anti-inflammatory, neuroprotective, and anti-apoptosis activities (41). The hepatoprotective effect of PNG was evaluated in APAP-induced liver damages (42). It showed that PNG treatment decreased AST, ALT, TNF-α, IL٦- and IL١-β levels in the liver. Also, PNG pre-treatment enhanced the activity of GSH and SOD while decreasing MDA production. This flavonoid could also up-regulate two important APAP detoxification enzymes including UDP glucuronosyltransferase 1 family polypeptide A1 (UGT1A1) and Sulfotransferase 1A1 (SULT1A1). PNG presented alleviative effects through activation of Nrf2 and PPARα signaling pathways (42).

Kaempferol (KF, 14) is a natural flavonol that can be obtained from *Kaempferol galanga* L (43). KF exhibits a broad spectrum of pharmacological effects, encompassing neuroprotection, antibacterial properties, anticancer activities, and anti-inflammatory actions (43). Recently, the protective role of KF was examined regarding liver damage caused by APAP (44). It was observed that this flavonoid restored liver damage and inflammatory reactions in APAP-exposed mice and amended hepatic iron excess and oxidative stress. *In vitro* test revealed that KF reversed the GSH depletion and cell viability while decreasing ROS accumulation. KF triggered the Nrf2 pathway and increased Gpx-4 levels in mouse livers and L02 cells to prevent ferroptosis caused by APAP (44).

Xanthohumol (XH, 15) is a prenylated flavonoid derived from Hops (*Humulus lupulus*). It possesses anticancer, antidiabetic, and anti-hyperlipidemia properties (45). The hepatoprotective role of XH was investigated against APAP-induced liver injury (46). It was observed that XH triggered Nrf2 activation through the AMPK/Akt/GSK3β signaling pathway to exert a cytoprotective effect. This compound notably reduced the levels of MDA, ALT, and AST while increasing the GSH content and survival rate of mice (46).

Puerarin (PR, 16), an important flavonoid derived from the roots of *Pueraria lobata*, exhibits a diverse array of pharmacological effects, including cardioprotection, antidiabetic properties, anti-Parkinson's effects, and anti-inflammatory actions (47). In 2020, the protective effect of PR was investigated against APAP-induced liver toxicity (48). It was observed that PR improved the cell activity of HepG2 cells, decreased the ROS accumulation and alleviated mitochondrial dysfunction. In addition, PR enhanced the levels of GCLC, GCLM, HO-1 and NQO1 through activation of the Keap1/Nrf2 signaling pathway (48).

Isorhamnetin (IR, 17) is a natural flavonol aglycone found in *Hippophae rhamnoides* L. IR possesses extensive properties, including cardiovascular protection, anti-inflammatory, antiapoptotic, and anticancer effects (45). The possible effect of IR in prevention of APAP-induced acute liver toxicity was evaluated. It was observed that IR decreased serum levels of ALT, AST, and ALP in treated animals. In addition, this flavonoid lessened the levels of NLRP3 and MPO and enhanced the activity of SOD. IR ameliorated histopathological alteration of the liver and elevated the levels of Nrf2 and Sirtuin 1 (49). In similar research the lipid-lowering, anti-inflammatory, and hepatoprotective action of IR on APAP-induced hepatotoxicity was reported (50). IR treatment significantly regulated the levels of TG and High-Density Lipoprotein (LDH).

Orientin (OR, 18) is a flavone glycoside that mostly obtained from *Ocimum sanctum*, *Phyllostachys* and *Passiflora* species. It has numerous therapeutic properties, including neuroprotective, vasodilatation, cardioprotective and anti-aging (51). The protective role of OR against APAP-induced oxidative stress

and mitochondrial dysfunction impairment in the liver was examined (52). OR markedly increased the levels of CAT, GSH, and SOD in the liver and kidneys. Moreover, results displayed that OR decreased mouse mortality and inhibited the expression of CYP2E1. OR averted APAP-induced hepatocyte damage via activation of Nrf2 signaling pathway and its related antioxidant proteins, including HO-1, GCLC, GCLM, and NQO1. Moreover, OR protected liver cells *via* inhibition of JNK/cytochrome c/caspase-3 signaling pathways (52).

Sappanone A (SA, 19) is a homoisoflavonoid isolated from *Caesalpinia sappan*. It has wide range of pharmacological activity such as anti-inflammatory, renal and cardiac protection (53). The ameliorative effect of SA on APAP-induced acute liver injury was explored (54). SA pretreatment dose dependently reduced the liver damage, as validated by reduced ALT/AST levels and histopathologic lesions. Also, the levels of pro-inflammatory cytokines, NAPQI, and MDA were reduced and content of GSH was increased. Mechanistically, SA could facilitate the nuclear translocation of Nrf2 (54).

Naringin (NG, 20) is a flavonoid produced in grapefruit and various citrus fruits. It is an anti-inflammatory, antioxidant, and neuroprotective compound. The ameliorative effect of NG against APAP-induced acute liver damage in mice was investigated (55). NG pretreatment increased the levels of antioxidant enzymes, suppressed pro-inflammatory cytokine production, and triggered apoptotic pathways. It was noted that NG effectively activates cation transport regulator-like protein 2 (CHAC2) and Nrf2 (55).

Glabridin (GR, 21) is an active ingredient obtained from the *Glycyrrhiza glabra* root. This compound has a wide range of pharmacological properties, such as anti-osteoporosis, anti-inflammatory, anti-bacterial, and anticancer (56). Alleviative property of GR on APAP-induced hepatic injury was studied (57). Histopathological evidence exhibited the shielding effect of GR on rat liver tissue damaged by APAP. This isoflavane activated the keap1-Nrf2-ARE pathway. GR enhanced the levels of GST, CAT, SOD, Gpx and GSH and reduced the level of MDA. Also, inflammatory markers including TNF-α, IL-6, and IL-1β were diminished in treated animals. Moreover, the protective role of GR against liver injury caused by APAP can be attained through the stimulation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt/Nrf2/HO-1) signaling pathway (57).

Baicalin (BCA, 22) is the major bioactive flavone separated from the root of *Scutellaria baicalensis*. It has several biological activates such as anti-inflammatory, antioxidant, anticancer and antivirus. Protective effects of BCA and its aglycone baicalein (BCE) against APAP-induced hepatotoxicity was investigated (58). It showed that these compounds are able to improved liver regeneration after APAP-induced acute liver injury. BCA and BCE diminished the level of ALT and AST and enhanced the cell survival and GSH content in hepatocytes. The involved mechanism of BCA and BCE-provided protection is the same, Nrf2 and its downstream GCLC/GCLM and NQO1 are critical for their protection (58).

Apigenin (API, 23), a flavonoid found in certain fruits, vegetables and herbs, acts as antimicrobial, anti-inflammatory and anti-mutagenic (59). The beneficial function of API in APAP-induced hepatotoxicity was demonstrated (60). The findings showed that API diminished the levels of ALT, AST, MDA, MPO, and ROS. Also, API activate the Sirtuin1 (Sirt-1)/Nrf2 signaling pathway. In addition, API reduces APAP-induced liver damage by activating the AMPK/GSK3β signaling pathway (60).

Farrerol (FR, 24) is a typical natural flavanone isolated from rhododendron. This active ingredient has several pharmacological properties, including antioxidant, anti-inflammatory, cardioprotective, anticancer, and anti-fungal (61,62). The hepatoprotective effect of FR on liver injury induced with APAP was explored in mice and HepG2 cells. It was confirmed that FR decreased oxidative stress through the activating of Nrf2 and inducing HO-1 expression. FR prevented mitochondrial damage in HepG2 cells by suppressing JNK phosphorylation, cytochrome c release and Bax mitochondrial translocation. *In vitro* results showed that induction autophagy via the AMPK/AKT pathway by FR contributed to its hepatoprotective activity (61).

Licochalcone A (LA, 25) is a flavonoid synthesized in the roots of *Glycyrrhiza uralensis*. LA has diverse biological activities including anti-parasitic, antibacterial, anticancer, and anti-inflammation properties (63). The alleviative effect of LA was

explored against APAP-induced hepatotoxicity (64). It was demonstrated that LA decreased the levels of MDA, ALT, AST, and tert-butyl hydroperoxide (t-BHP). Also, this active ingredient decreased the cell apoptosis, histopathological damage and lethality in mice. *In vitro* findings revealed that LA treatment improved the Keap1-Nrf2/ARE antioxidative signaling pathway in HepG2 cells (64).

Isoorientin (ISO, 26) is a natural *C*-glucosyl flavone that separated from various plant species, such as *Phyllostachys pubescens* and *Patrinia spp*. Investigations have verified anti-inflammatory, antioxidant, antinociceptive and nephroprotective effects of ISO (65,66). Ameliorative effect of this medicinal compound was evaluated against APAP-induced hepatotoxicity. ISO not only diminished the levels of ALT, AST, MDA, and MPO, but also enhanced the levels of GSH and SOD. Hepatoprotective effect of ISO mediated by activating Nrf2 *via* the AMPK/Akt/GSK3β pathway (67).

Formononetin (FMN, 27) is an isoflavone from the group of phytoestrogens that presented a broad range of pharmacological effects (68). This compound has antiapoptotic, anti-inflammatory, and anti-hyperglycemic effects. The role of FMN against APAP-induced liver injury was explored (69). It was exhibited that supplementation with FMN remarkably reduced the levels of MDA, ALT, AST and increased the content of GSH in mice. FMN diminished hepatocellular damage and cell apoptosis and increased the activity of Nrf2 (69).

Quercitrin (QC, 28) is a plant flavonoid found in many fruits and vegetables. This flavonoid has antioxidant, immunomodulation, anti-inflammation and wound healing properties (52). In a study, hepatoprotective mechanism of QC in mice and HepG2 cells was indicated (70). QC not only alleviated liver necrosis, but also decreased the level of pro-inflammatory factors including IL-1β, COX-2, and inducible Nitric Oxide Synthase (iNOS). Additionally, QC enhanced the levels of Nrf2, NQO1, CAT, Gpx, and SOD-2 (70).

Confusoside (CF, 29) is a dihydrochalcone glycoside presented in the leaves of *Anneslea fragrans*. It has excellent anti-inflammatory and antioxidant effects (71). A recent report highlighted the preventive role of CF in protecting mice from liver damage induced by APAP (71). CF successfully lowered the serum levels of ALT, AST, and LDH. This NC may boost Nrf2 activity, which would increase the levels of its downstream enzymes, such as NQO1 and HO-1. Additionally, CF may suppress the liver's inflammatory response by blocking the activation of the NF-κB signaling pathway, resulting in reduced expressions of IL-6, TNF-α, IL-1β, and NO (71).

Diacerein (DIA, 30) is a natural anthraquinone that is applied for the treatment of osteoarthritis. A recent study revealed that DIA has protective effect against APAP-induced liver injury (2). This herbal compound diminished the levels of inflammatory cytokines and enhanced the levels of Nrf-2, SOD, HO-1and GSH. The result of this study showed that DIA protect liver though the inhibition of JNK- mediated oxidative stress and apoptosis (2). Emodin (EMD, 31) is a natural bioactive compound that isolated from the plant *Rheum palmatum* L. This anthraquinone has diverse biological activity including anti-inflammatory, antioxidant, anticancer and neuroprotective effects (72). A study evaluated the effect of EMD on APAP-induced hepatotoxicity. The results exhibited that EMD regenerated hepatocytes by alleviating pathological injury, apoptosis, and oxidative stress. EMD diminished the expression of NLRP3 and lowered the levels of pro-inflammatory factors. Furthermore, it has an inhibitory effect on Interferon (IFN)-α, cyclic GMP-AMP synthase (cGAS), and the downstream signaling effector Stimulator of Interferon Genes (STING) expression to protect the hepatocytes from APAP-induced inflammatory responses and apoptosis. EMD alleviated APAP-induced liver injury by activating Nrf2 signaling pathway and inhibiting the NLRP3 inflammasome and cGAS-STING signaling pathway (72). Shikonin (SHK, 32) is the major active ingredient derived from the roots of medicinal plants such as *Lithospermum erythrorhizon*. SHK has several therapeutical benefits such as neuroprotective, wound healing, anticancer and anti-inflammation (73). Li and co-workers explored the protective effect of SHK in APAP-induced liver toxicity. They observed that SHK defended APAP-induced liver toxicity via decreasing serum ALT/AST, liver MPO activity, and ROS. Also, this compound reduced the cell mortality and prevented GSH depletion. It was revealed that

SHK inhibits APAP hepatotoxicity liver toxicity by enhancing Nrf2 through the PI3K/Akt/GSK-3β signaling pathway (73).

Terpenoids

Terpenoids are the largest class of natural products. They are classified as monoterpenes (10 C), sesquiterpenes (15 C), diterpenes (20 C), sesterterpens (25 C), triterpenes (30 C), tetraterpenes (40 C) and polyterpenes (> 40 C). Their biological activities have been reported (74). Especially, the hepatoprotective effects of terpenoids have well documented in previous studies (75, 76).

Carveol (Car, 33) is a monoterpenoid derived from plant species such as *Illicium pachyphyllum* and *Cymbopogon giganteus*. It has long been used as an antihyperlipidemic, antispasmodic, and antioxidant (77). Rahman and co-workers conducted a study for clarifying the protective effects of Car on APAP-induced liver damage (77). Molecular and *in silico* approaches were showed that Car could acts as a strong antioxidant and anti-inflammatory factor that boosted protective properties. It was observed that Car significantly decreased the toxic effects of APAP by enhancing the activity of the Nrf2 and its downstream antioxidant enzymes and also may be related with the negative modulation of p-JNK (77).

Abietic acid (AA, 34), as a natural diterpenoid, occurs in pine woods. This compound has anti-edematogenic and analgesic activities (78). The alleviative effect of AA was exhibited against APAP-induced liver injury in mice (79). APAP could increase Fe^{2+} level and decreased ATP, GSH, and Gpx٤- levels. AA blocked APAP-triggered NF-κB activation, ferroptosis and enhanced the levels of Nrf2 and HO-1. It was revealed that AA inhibited APAP hepatotoxicity by reducing inflammation and ferroptosis *via* the regulation of the Nrf2/HO-1 pathway (79).

Kahweol (KW, 35) is the major diterpenoid presents in coffee beans. This active compound has antidiabetic, anticancer and anti-inflammatory effects (80). Recently, the action of KW on APAP hepatotoxicity was explored (81). Administration of KW lessened the levels of liver injury enzymes and alleviated histological damage in APAP-treated mice. KW inhibited Endoplasmic Reticulum (ER) stress, lipid peroxidation and nucleic acid oxidation. Also, this antioxidant enhanced the level of Nrf2 and restored GSH content (81).

Carnosic acid (CAN, 36) is a diterpenoid produced by rosemary. It has neuroprotective, anti-inflammatory, anticancer and anti-oxidative properties (82). CAN treatment significantly alleviated APAP-induced hepatic necrosis in mice. It significantly inhibited pro-inflammatory cytokines and LDH release. Histological finding revealed that this NC considerably improved APAP-induced hepatic necrosis. This bioactive compound prevented the accumulation and formation of ROS and additionally inhibited the activation of JNK. CNA promoted Nrf2 nuclear translocation, resulted in the induction of Nrf2-dependent enzymes such as Gpx and SOD (83).

Tanshinone IIA (TIIA, 37) is the primary active ingredient found in *Salvia miltiorrhiza*. This diterpenoid exhibits various biological activities, including antioxidant, anticancer, and protection of endothelial cells (84,85). It was revealed that TIIA pretreatment diminished APAP-induced hepatotoxicity. This compound was able to activate Nrf2 and elevated the levels of Nrf2 target enzymes, including GCLC, NQO1 and HO-1 (84). In other study, it was showed that TIIA increased the levels of multidrug resistance-associated protein (Mrp) 2 and Mrp4. *In vitro* experiments revealed that enhanced the expression of Mrp2 and Mrp4 by a mechanism that inhibits the expression of HOX transcript antisense RNA (HOTAIR), a type of long non-coding RNA (86).

Andrographolide (AGL, 38), being a triterpenoid, is an active ingredient extracted from *Andrographis paniculata* (Acanthaceae). It has diverse pharmacological effects, including hepatoprotective, antibacterial, anti-inflammatory and antitumor. Previous studies have shown that long term APAP use can lead to hepatic collagen deposition and Hepatic Stellate Cells (HSCs) activation (87,88). This condition may result in liver fibrosis. In a study, the alleviative effect of AGL was investigated in APAP-induced liver fibrosis in C57BL/6 mice (89). AGL facilitated Nrf2 nuclear translocation and increased the level of Nrf2 downstream antioxidant enzymes including NQO1 and HO-1 (89).

Ginsenoside Rg1 (GRg1, 39) is a major active constituent of ginsenosides, that is a perennial

medicinal plant belonging to *Araliaceae* family. This triterpenoid has several biological activities including antidepressant, anti-inflammatory, neuroprotective and hepatoprotective activities (90). A study demonstrated that GRg1 suppressed the activities of CYP2E1, CYP3A11, and CYP1A2, which are essential enzymes in the formation of NAPQI (91). Moreover, *via* activation of Nrf2, GRg1 reduced MDA and increases SOD, CAT and GSH. Compound GRg1not only enhanced the capacity of antioxidant and detoxification enzymes, but also increased the levels of HO-1 and NQO1 (91).

Limonin (LN, 40) is a natural triterpenoid that exist in plants such as *Euodia rutaecarpa* and *Phellodendron chinense* Schneid. It exhibits a broad range of therapeutic effects, including analgesic, antimicrobial, anti-inflammatory, and anticancer properties (92). The ameliorative effect of LN was studied against hepatotoxicity of APAP (13). Results revealed that LN enhanced the cell viability and improved Mitochondrial Membrane Potential (MMP) in L-02 cells. Additionally, LN led to the activation of Nrf2 and elevated the levels of its downstream targets, which include HO-1, NQO1, and GCLC/GCLM. It was demonstrated that LA suppressed the NF-κB inflammatory response by enhancing Sirt-1 levels (13).

Astragaloside IV (AS-IV, 41) is the active ingredient derived from *astragalus membranaceus* Bunge. Compound AS-IVhas remarkable protective effects on the cardiovascular and immune systems. The protective effect of this triterpenoid was shown on APAP-induced liver failure. AS-IV protects liver by inhibition of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α. In addition, AS-IV enhanced the level of Nrf2, HO-1 and diminished the level of NQO1 (93).

Esculentoside A (EsA, 42) is a triterpenoid obtained from the roots of *Phytolacca esculenta*. It has been demonstrated to possess anti-inflammatory, anticancer, and antifungal properties (94). The hepatoprotective effect of EsA against APAP-induced liver damage was examined both *in vitro* and *in vivo* (94). It was observed that EsA decreased the centrilobular necrosis and ALT and AST levels in treated animals. Also, this triterpene glycoside inhibited cytotoxicity, GSH depletion and apoptosis in APAP-exposed HepG2 cells. EsA inhibited Bax mitochondrial translocation as well as mitochondrial inter-membrane protein release. EsA protect liver cells through the activation of Nrf2 and AMPK/Akt/GSK3β pathway (94).

Astaxanthin (ASX, 43) is a xanthophyll carotenoid with beneficial effects on human health. This tetraterpenoid has antidiabetic, immuno-modulation, anti-hypertension, and anticancer properties (95). The ameliorative effect of ASX against APAP-induced liver injury was explored (96). ASX is practically insoluble in water. To solve this problem, ASX was loaded on the hollow mesoporus silics nanoparticles to enhance its water solubility. It was observed ASX activated the Nrf2/HO-1 pathway and enhanced autophagy and inhibited ferroptosis. This antioxidant increased the level of HO-1, CAT and Gpx-4 and lowered the levels of AST, ALT, IL-1β and IL-6 (96).

Alkaloids

Alkaloids are a class of natural products containing at least one nitrogen atom in the structure (97). Rutaecarpine (Rutc, 44) is an alkaloid has been used against postpartum hemorrhage, high blood pressure, abdominal pain and amenorrhea. It was observed that Rutc has protective effect in liver of APAP-intoxicated mice (11). APAP intoxication resulted in ROS generation in mitochondria and sustained activation of JNK. Rutc pretreatment restrained APAP-induced expression of inflammatory cytokines through inhibiting NF-κB activation by JNK1/2. Compound Rutc could decrease the activity of liver enzymes and content of MDA and prevent depletion of GSH. Also, Rutc increases the Nrf2 and its related enzymes including NQO1 and HO-1 (11).

Nicotinic acid (NA, 45), as an alkaloid, has numerous pharmacological properties including reno-protective, hepatoprotective, antioxidant and lipid-lowering. Recently, the role of NA against hepatotoxicity of APAP in BALB/c mice was evaluated (98,100). The findings indicated that pretreatment with NA markedly enhanced the survival rate of animals and reduced the levels of ALT, AST, and MDA. Moreover, the activities of SOD, CAT and GSH content were enhanced. NA protect liver by activation of Sirt-1/Nrf2 axis (98).

Berberine (BBR, 46) is an isoquinoline alkaloid

sourced from the medicinal herb Rhizoma coptidis. It possesses numerous therapeutic benefits including antibacterial, antineoplastic, anti-inflammatory, and cholesterol-reducing effects (99). Results showed that BBR significantly improved APAP-caused damage in C57BL/6 mice. This compound markedly influenced APAP-induced liver damage by reducing oxidative stress, liver cell death, and inflammatory response. BBR reduced APAP-induced damage by inhibiting JNK phosphorylation and increasing nuclear Nrf2 expression. Moreover, BBR evidently prevented infiltration of macrophages and neutrophils as well as DNA fragmentation (99).

Nitrile containing compounds

Sarmentosin (SM, 47) is a nitrile containing glycoside isolated from medicinal herb *Sedum sarmentosum*. This compound has biological properties such as anticancer, hepatoprotective, anti-inflammatory, and anti-fibrotic (100). The role of SM on APAP-induced acute liver failure was determined. It was revealed that SM promoted accumulation of Nrf2 *via* upregulating USP17-mediated ubiquitin inhibition. In addition, the level of mitophagy was increased in this process. Mitophagy helps to mitochondria function and ROS homeostasis, by removal of ROS- damaged mitochondria. SM could alleviate APAP-induced liver injury by USP17-mediated Nrf2 overexpression and PTEN-Induced Kinase 1 (PINK1)-dependent mitophagy (100).

Amygdalin (AD, 48) is a cyanogenic glucoside extracted from *Bitter Apricot* seed. It has immunomodulatory, analgesic and antitumor effects (101). The protective effect of AD against APAP-induced acute liver failure was investigated in animal model. Findings showed that this active component can reduce the levels of liver enzymes and necrosis. In addition, AD diminished the inflammatory cytokines level, SOD activity and MDA content. It was demonstrated that AD has protective effect by activating the AKT/JNK/Nrf2 pathway (102).

Organo-sulfur compounds

Organo-sulfur compounds are organic molecules containing sulfur which are associated with the pungent odors (103). Sulforaphane (SFN, 49) is an organo-sulfur compound that mainly produced in cruciferous vegetables. SFN possesses broad spectrum of bioactivity including antitumor, anti-angiogenic, and anti-inflammatory agent (56). The alleviative effect of SFN was assessed against hepatotoxicity of APAP. It was noted that treatment for a short duration (≤3 *hr*) with SFN alone did not activate Nrf2 or its target components. The result of this study revealed that Nrf2 activators possess intrinsic issues. They must induce cellular stress to trigger Nrf2 and delayed adaptive responses, which may impede long-term protection against APAP-related liver toxicity (104).

Allyl isothiocyanate (ALI, 50) is an herbal compound belonging to the Cruciferae family. ALI has many medicinal effects including anti-inflammatory, anticancer, anti-bacterial and antidiabetic (31,105). Beneficial effects of ALI on hepatocytes in animal model was indicated (106,107). Kim and co-workers have presented that ALI protects the liver against APAP-induced injury (105). This organosulfur compound prevents the degradation of Nrf2. In addition, ALI increases the expression of Nrf2 target genes (such as HO-1) (105).

Allyl methyl trisulfide (AMT, 51) is a volatile organosulfur compound of garlic (*Allium sativum L.*). Like the other medicinal plants such as Jujuboside B, AMT has anti-inflammatory, hepatoprotective and antioxidant effects (108-110). The protective role of AMT was studied in APAP-received animals. It was observed that AMT attenuated APAP-induced hepatotoxicity by reduction of MDA level and serum ALT and AST activities and improvement of liver histological morphology. In addition, AMT treatment resulted in enhancement of NQO1, γ-GCS, HO-1, and SOD. This compound could attenuate APAP-induced hepatotoxicity by suppressing CYP2E1 and activating Nrf2 (108). NPs that ameliorate APAP-induced hepatotoxicity through the Nrf2/Keap1/ARE signaling pathway (Table 2).

Chemical structures of compounds with hepatoprotective effect against acetaminophen-induced toxicity are shown in figure 3.

Conclusion and future prospective

APAP is the most commonly taken analgesic drug. It is the number one cause of ALF worldwide. NAPQI, an electrophilic metabolite, is responsible for hepatotoxicity of APAP. Although NAC is the major

Table 2. Summary of the protective effect of NPs against APAP-induced hepatotoxicity by activating the Nrf2 pathway

Category	Compound	Animal/cell line	APAP dose/ route	NPs dose/ route	Molecular tests	Ref
Phenolic compounds	Urolithin A (1)	Male C57BL/6J	500, 750 *mg/kg, i.p.*	50,100,150 *mg/kg i.p.*	Keap1, ALT, AST, LDH Nrf2, Mitophagy, HO-1, NQO1	(18)
	Rosmarinic acid (2)	Male Kunming mice	500 *mg/kg, i.p.*	20, 40, 80 *mg/kg, i.p.*	MDA, IL-1β, IL-18, ALT, AST Nrf2, SOD, GSH, Gpx, HO-1	(20)
	Gastrodin (3)	Adult C57BL/6 (B6) mice	300 *mg/kg, i.p.*	0, 15, 30, 45 *mg/kg, i.p.*	MDA, TNF-α, IL-1β, IL-6, MPO, ALT Nrf2, SOD	(23)
	Sinapic acid (4)	Male C57BL/6 mice	300 *mg/kg, i.p.*	10, 50 *mg/kg*, orl.	ALT, ALP, AST, ROS, MDA, IL-6, TNF-α, NF-κB, MPO, cathepsin B, β-galactosidase Nrf2, Sirt-1, HO-1, SOD	(25)
	Chlorogenic acid (5)	Male C57BL/6 mice	300 *mg/kg,* orl.	10, 20, 40 *mg/kg,* orl.	hepatic infiltration, HMGB1, HSP60 Nrf2, (Lon) protein	(28)
	Guavinoside B (6)	C57BL/6 male mice	300 *mg/kg, i.p.*	100 mg/kg, gavage	AST, ALT, ROS, MDA, TNF-α, JNK Nrf2, GSH, SOD, GCLC, NQO1	(4)
	Honokiol (7)	Male Balb/c mice	200 *mg/kg, i.p.*	100 *mg/kg*, gavage	CYP 2E1, CYP2A1 Nrf2, GSH, GCLC, GST, GCLM	(12)
	Tovophyllin A (8)	Male BALB/c mice	100 *mg/kg, i.p.*	50, 100 *mg/kg*, olr.	NF-κB, TNF-α, IL-1β, IL-6 Nrf2, HO-1, SOD, GCLC, GCLM	(3)
	Corilagin (9)	Male C57BL/6 mice	900 *mg/kg i.p.*	15, 30, 60 *mg/kg, i.p.*	ROS, Keap1, ALT, AST, MPO, MDA, JNK, AMPK, GSK3β, LKB1 Nrf2, ARE, SOD, GSH-to-GSSG,	(32)
	Salvianolic acid C (10)	Adult male ICR mice	400 *mg/kg, i.p.*	5,10, 20 *mg/kg, i.p.*	AST, ALT, TC, T-Bil, TG, MDA, NF-κB, MAPK, TRL4 Nrf2, GSH, Gpx, HO-1	(33)
	Salvianolic acid B (12)	Male Kunming mice	300 *mg/kg, i.g.*	25-50 *mg/kg, i.g.*	AST, ALT Nrf2, GSH, HO-1, GCLC	(37)
	Pectolinarigenin (13)	Male C57BL/6 mice	400 *mg/kg, i.p.*	5, 10 *mg/kg, i.p.*	AST, ALT, TNF-α, IL-6, IL-1β, MDA Nrf2, UGT1A1, SULT1A1, GSH, SOD	(42)
	Kaempferol (14)	Male BALB/c mice	250 *mg/kg, i.p.*	40, 80 *mg/kg, i.g.*	Feroptosis, ROS, ALT, AST Nrf2, GSH, Gpx-4	(44)
	Xanthohumol (15)	Female C57BL/6 J mice	900 *mg/kg, i.p.*	50 *mg/kg, i.p.*	ALT, AST, MDA Nrf2, SOD, GSH, HO-1, GCLC, NQO1, Bcl-2, AKT, GSK3β	(46)
	Puerarin (16)	SPF ICR mice	300 *mg/kg, i.g.*	200, 400, 800 *mg/kg, i.g.*	MDA, AST, ALT, AKP, γ-GT, TBIL, Keap1 Nrf2, CAT, GSH, SOD, GCLC, GCLM, HO-1 NQO1	(48)

Contd. table 2.

Isorhamnetin (17)	Balb/C mice	300 *mg/kg, i.p.*	25, 100 *mg/kg*, orl	ALT, AST, ALP, ROS, TBARS, IL-6, TNF-α, NF-κB NLRP3, Caspase-1, MPO Nrf2, GSH, SOD, Sirt-1	(49)
Orientin (18)	Male C57BL/6 mice	400 or 900 *mg/kg, i.p.*	12.5, 25, 50 *mg/kg, i.p.*	CYP2E1, ALT, AST, MPO, MDA, JNK, Bax, Caspase-3 Nrf2,SOD, GSH-to-GSSG, HO-1, GCLC, GCLM, NQO1, Bcl-2	(52)
Sappanone A (19)	C57BL/6 N mice	300 *mg/kg, i.p.*	25, 50, 100 *mg/kg, i.p.*	ALT, AST, NAPQI, MDA, TNF-α, IL-1β Nrf2, GCLM, GCLC, HO-1, NQO1, GSH	(54)
Naringin (20)	C57BL/6 mice	400 *mg/kg, i.p.*	30, 60,120 *mg/kg*, orl	MDA, TNF-α, IL-1β, ALT, AST Nrf2, SOD, HO-1	(55)
Glabridin (21)	Male Sprague-Dawley rats	500 *mg/kg, i.p.*	30 *mg/kg*, orl	AST, ALT, ALP, TNF-α, IL-6, ,MDA, Caspase-3, Caspase-9, Bax Nrf2, CAT, Gpx, SOD, GST, GSH, PI3K, Akt, HO-1, Bcl-2	(57)
Baicalin (22)	Male C57BL/6 mice	300 *mg/kg,* orl	40, 80 *mg/kg*, orl	ALT, AST, MPO, ROS Nrf2, GCLC, GCLM, NQO1	(58)
Apigenin (23)	C57BL/6J mice	300 *mg/kg*, orl	20, 80 *mg/kg*, orl.	ALT, AST, MPO, ROS Nrf2, CPT1A, AMPK, GSK3β,	(60)
Farrerol (24)	Female B6 mice	400 or 900 *mg/kg, i.p.*	40 *mg/kg, i.p.*	Mortality, cytochrome c, ALT, AST, JNK Nrf2, autophagy	(61)
Licochalcone A (25)	C57BL/6 mice	400 or 900 *mg/kg i.p.*	50,100 *mg/kg i.p.*	MDA, IL-1β, IL-18, ALT, AST, Bax, Caspase-3, JNK Nrf2, SOD, Bcl-2, GSH-to-GSSG, GCLC, GCLM, MPO, HO-1	(64)
Isoorientin (26)	C57BL/6J mice	400 or 900 *mg/kg*	50 *mg/kg i.p.*	ALT, AST, MPO, MDA, SOD, JNK, Bax Nrf2, GSH, AMPK, Akt, GSK3β	(67)
Formononetin (27)	Male BALB/c mice	300 *mg/kg, i.p.*	50, 100 *mg/kg i.p.*	ALT, AST, MDA, apoptosis Nrf2, GSH, CAT, NQO1, Gpx -1, SOD	(69)
Quercitrin (28)	Male Balb/c mice	300 *mg/kg*, orl	10, 50 *mg/kg,* orl	ALT, AST, NO, COX-2, IL-1β, p38, JNK Nrf2, NQO1, CAT, Gpx, SOD-2	(70)
Confusoside (29)	Male Kunming mice	300 *mg/kg, i.g.*	20, 60 *mg/kg, i.p.*	TNF-α, IL-1β, IL-6, NO, AST, ALT, LDH Nrf2, NQO1, HO-1, SOD, CAT	(71)

Contd. table 2

Diacerein (30)	C57BL/6 mice	400 *mg/kg, i.p.*	25,50 *mg/kg*, gavage	ALT, AST, JNK, MDA, Bax, Caspase-3 Nrf-2, SOD, HO-1, NQO1, GSH, Bcl-2	(2)
Emodin (31)	C57BL/6 mice	300 *mg/kg, i.p.*	15, 30 *mg/kg*, orl	ALT, AST, ALP, MDA, NLRP3, IL-1β, IL-6,TNF-α, cGAS, STING Nrf2, albumin, GSH, SOD, HO-1, NQO1	(72)
Shikonin (32)	C57BL/6 mice	10 *Mm/* (500 *mg/ kg, i.p.*	0.375, 0.5 *μM/* 12.5, 25.0 *mg/kg i.p.*	AST, ALT, MPO, GSK3β Nrf2, GSH, PI3K, Akt	(73)
Carveol (33)	Male BALB/c mice	400 *mg/kg, orl*	5,10,15 *mg/kg, i.p.*	LPO, TNF-α, NF-κB, IL-1β, LPO Nrf2, GSH, GST, HO-1	(77)
Abietic acid (34)	Male C57BL/6 mice	300 *mg/kg, i.p.*	10, 20, 40 *mg/kg, i.p.*	ALT, AST, MPO, MDA, Iron content, TNF-α, IL-1β Nrf2, GSH, ATP, HO-1	(79)
Kahweol (35)	C57BL/ 6Nmice	400 *mg/kg, i.p.*	20 *mg/kg, i.p.*	LPO, nucleic acid oxidation, NF-κB, infiltration of neutrophils and macrophages, ER stress, Keap1 Nrf2, GSH, SOD-2, Gpx-1, GCLC, GCLM	(81)
Carnosic acid (36)	Male C57BL/6J mice	400 *mg/kg, i.p.*	100 *mg/kg*, gavage	ALT, AST,TNF-α, JNK, MDA, LDH, ROS, IL-1β, IL-6 Nrf2, HO-1	(83)
Tanshinone IIA (37)	Male C57BL/6J mice	200 *mg/kg*, gavage	30 *mg/kg*, orl	ALT, AST, NAPQI Nrf2, Mrp2, Mrp4	(86)
Andro-grapholide (38)	C57BL/6 mice	300 *mg/kg, i.g.*	20, 40 *mg/kg, i.g.*	Keap1, HSCs Nrf2, NQO1, HO-1	(89)
Ginsenoside Rg1 (39)	Male C57BL/6 mice	400 *mg/kg, i.p.*	15,30 or 60 *mg/kg, i.p.*	Keap1, CYP2E1, CYP 3A11, CYP 1A2 Nrf2, GCLC, GCLM, HO-1, NQO1, UGT1A1, UGT1A 6, UGT 2B1, SULT2A1, Mrp2, Mrp3, Mrp4	(91)
Limonin (40)	L-02 cells	7.5 *mM*	10, 25, 50 *μM*	NF-κB, TNF-α, ROS, iNOS, COX-2, IL-1β, IL-6. Nrf2, Sirt-1, HO-1, NQO1, GCLC, GCLM	(13)
Astragaloside IV (41)	Male ICR mice	400 *mg/kg,* orl	20, 40 *mg/kg*, orl	ALT, AST, MDA, IL-1β, IL-6, TNF-α, Keap1 Nrf2, GSH, SOD, HO-1, NQO1	(93)
Esculentoside A (42)	Female BALB/c mice	400, 900 *mg/kg, i.p.*	2.5 *mg/kg, i.p.*	ALT, AST, JNK, Bax, MPO, AIF Nrf2, SOD, GSH, AMPK, Akt, GSK3β, HO-1	(94)

Contd. table 2.

	Astaxanthin (43)	Male C57BL/6 mice	500 *mg/kg, i.p.*	100 *mg/kg,* gavage	MDA, TNF-α, IL-1β, and IL-6, LPO, ALT, AST, CK, LDH Nrf2, SOD, GSH, Gpx	(96)
Alkaloids	Rutaecarpine (44)	Male ICR mice	300 *mg/kg*, orl	5, 20 *mg/kg*, orl	ALT, AST, CYP2E1, NF-κB Nrf2, GCLC, HO-1, NQO1	(11)
	Nicotinic acid (45)	BALB/c mice	400, 600 *mg/kg, i.p.*	100 *mg/kg, i.p.*	ALT, AST, MDA, Keap1 Nrf2, SOD, CAT, GSH, Sirt-1, NQO1	(98)
	Berberine (46)	Male C57BL/6 mice	500 *mg/kg, i.p.*	2, 5 *mg/kg, i.p.*	ALT, AST, MDA, MPO, JNK, HMGB1, Caspase-1, IL-1β Nrf2, GSH, UGT1A1, UGT1A6, SULT1A1	(99)
Nitrile containing compounds	Sarmentosin (47)	Male ICR mice	300 *mg/kg, i.p.*	20, 40, 80 *mg/kg, i.g.*	MDA, ALT, AST, ALP Nrf2, NQO1, HO-1, SOD, GSH/GSSG	(100)
	Amygdalin (48)	Male C57BL/6 mice	400 *mg/kg, i.p.*	2.5, 5 *mg/kg, i.p.*	ALT,AST, MPO IL-6, TNF-α, IL-1β, SOD, MDA, JNK Nrf2, NQO1, HO-1, Akt	(102)
Organo-sulfur compounds	Sulforaphane (49)	murine model	300 *mg/kg, i.p.*	5 *mg/kg, i.p.*	Nrf2, HO-1	(104)
	Allyl isothiocyanate (50)	C57BL/6 mice	250 *mg/kg, i.p.*	25,50 *mg/kg,* orl	ALT, AST,TNF-α, JNK Nrf2, HO-1	(105)
	Allyl methyl trisulfide (51)	75 KM mice	300 *mg/kg i.p.*	25, 50, 100 *mg/kg,* gavage	MDA, ALT, AST, CYP 2E1 Nrf2, NQO1, γ-GCS, HO-1, SOD	(108)

Abbreviations: i.p. : intraperitoneal ; i.g. : intragastrical; orl: orally; Nrf2; nuclear factor erythroid 2-related factor 2; UGT1A1: DP Glucuronosyltransferase Family 1 Member A1; SULT1A1: Sulfotransferase Family 1A Member 1; Bcl-2: B-cell lymphoma 2; AKT: Protein kinase B; GSK3β: Glycogen synthase kinase-3 beta; TBIL: total bilirubin; TBARS: Thiobarbituric acid reactive substances; Sirt 1: Sirtuin 1; CYP2E1: Cytochrome P450 2E1; MPO: Myeloperoxidase; JNK: c-Jun N-terminal Kinase; NAPQI: N-acetyl-p-benzoquinone imine; TNF-α: Tumor necrosis factor; NF-κB: Nuclear factor kappa B; NLRP3: NOD-like" receptor 3; Gpx-4: Glutathione peroxidase4; GCLC: gamma-glutamylcysteine synthetase; NQO1: NAD(P)H quinone oxidoreductase 1; gamma-glutamylcysteine synthetase; NAPQI: N-acetyl-p-benzoquinone imin, iNOS: inducible nitric oxide synthase; mrp: multi-drug resistance; COX-2: cyclooxygenase-2, CPT1A: carnitine palmitoyltransferase I; Ugt: UDP Glucuronosyltransferase; HSCs: hepatic stellate cells; HMGB1: High mobility group box 1; AIF; apoptosis-inducing factor; LKB1: Liver kinase B1.

treatment for APAP hepatotoxicity, it only works for a short period of time and causes vomiting and even shock in some patients.

The Nrf2/ARE signaling pathway is a crucial part of the body's natural antioxidant system. Natural products like glabridin (21), chlorogenic acid (5), and salvianolic acid B (12) have been reported for their considerable protective role against APAP-induced liver damage through the activation of the Nrf2 signaling pathway. Activation of Nrf2 leads to the production of its downstream enzymes, including SOD, CAT, Gpx, NQO1, and HO-1. Several natural products including phenolic, treponoids, alkaloids, nitrile containing compounds, and organo-sulfur compounds could provide a protective benefit against APAP-induced liver damage through the activation of the Nrf2 signaling pathway. However, despite promising preclinical outcomes, several limitations

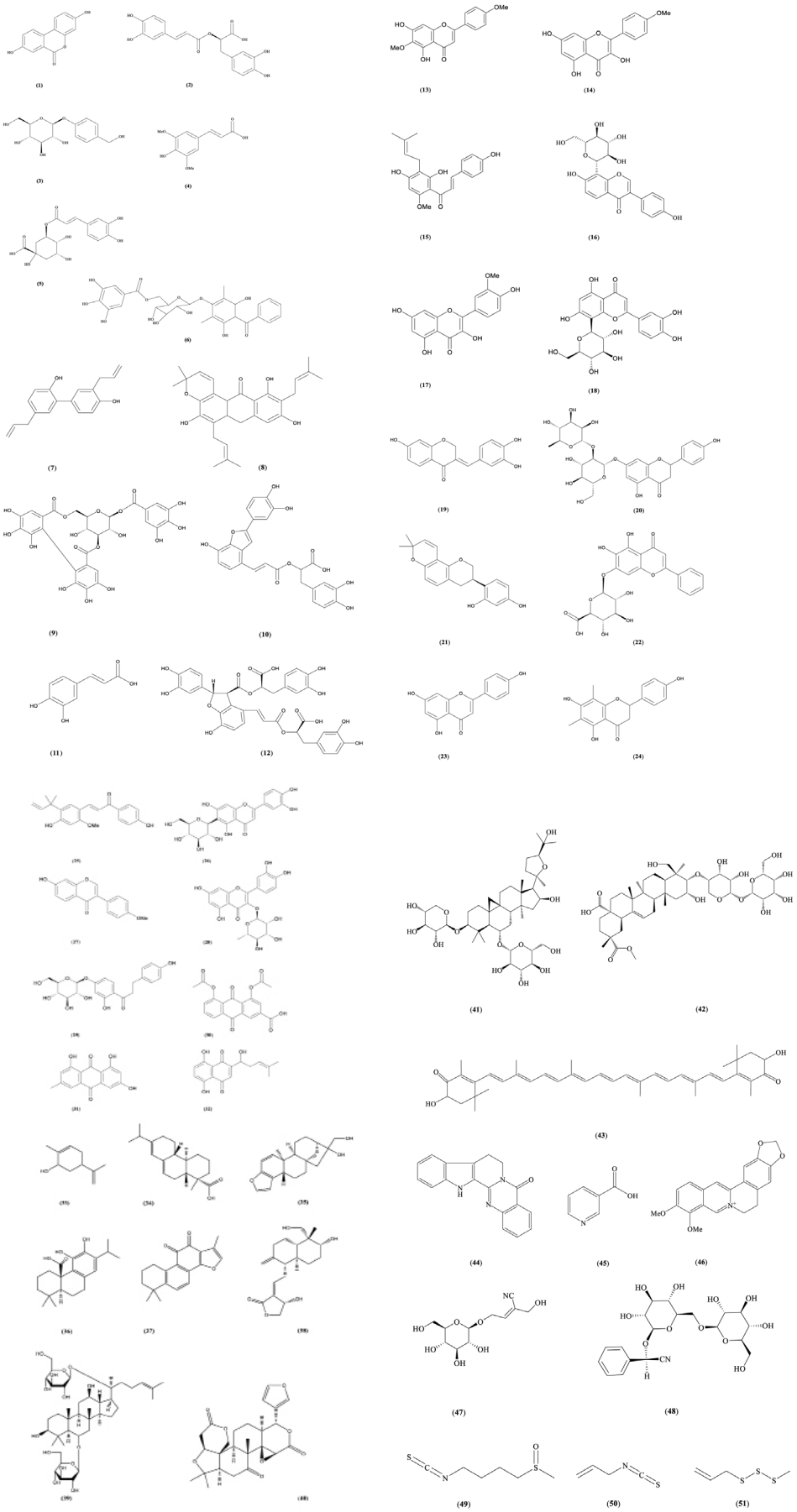


Figure 3. Chemical structures of compounds with hepatoprotective effect against acetaminophen-induced toxicity.

and safety concerns remain. The majority of evidence comes from studies involving animals or cells, and there is still a shortage of clinical data in humans. The bioavailability and metabolic stability of many phytochemicals are poor, which may restrict their clinical utility. Furthermore, some compounds, especially alkaloids and polyphenols, may show dose-dependent toxicity or interact with cytochrome P450 enzymes, thereby altering drug metabolism and possibly increasing APAP toxicity. Herb–drug interactions are another important concern, especially for patients receiving other hepatically metabolized drugs. Moreover, variations in plant sources, extraction techniques, and compound standardization present difficulties for reproducibility and translational potential.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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