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Dibenzocyclooctadiene lignans from the family Schisandraceae: A review of phytochemistry, structure-activity relationship, and hepatoprotective effects

Shi-qi Liu [a,1], Yu-pei Yang [a,1], Nusrat Hussain [b], Yu-qing Jian [a], Bin Li [a], Yi-xing Qiu [a], Huang-he Yu [a], Hui-zhen Wang [a], Wei Wang [a,*]

[a] TCM and Ethnomedicine Innovation & Development International Laboratory, School of Pharmacy, Hunan University of Chinese Medicine, Changsha 410208, China
[b] Department of Chemistry, University of Baltistan Skardu, Skardu 16100, Pakistan

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ABSTRACT

Liver injury is a common pathological process characterized by massive degeneration and abnormal death of liver cells. With increase in dead cells and necrosis, liver injury eventually leads to nonalcoholic fatty liver disease (NAFLD), hepatic fibrosis, and even hepatocellular carcinoma (HCC). Consequently, it is necessary to treat liver injury and to prevent its progression. The drug Bicylol is widely employed in China to treat chronic hepatitis B virus (HBV) and has therapeutic potential for liver injury. It is the derivative of dibenzocyclooctadiene lignans extracted from *Schisandra chinensis* (SC). The Schisandraceae family is a rich source of dibenzocyclooctadiene lignans, which possesses potential liver protective activity. This study aimed to comprehensively summarize the phytochemistry, structure-activity relationship and molecular mechanisms underlying the liver protective activities of dibenzocyclooctadiene lignans from the Schisandraceae family. Here, we had discussed the analysis of absorption or permeation properties of 358 compounds based on Lipinski's rule of five. So far, 358 dibenzocyclooctadiene lignans have been reported, with 37 of them exhibited hepatoprotective effects. The molecular mechanism of the active compounds mainly involves antioxidative stress, anti-inflammation and autophagy through Kelch-like ECH-associating protein 1/nuclear factor erythroid 2 related factor 2/antioxidant response element (Keap1/Nrf2/ARE), nuclear factor kappa B (NF-κB), and transforming growth factor β (TGF-β)/Smad 2/3 signaling pathways. This review is expected to provide scientific ideas for future research related to developing and utilizing the dibenzocyclooctadiene lignans from Schisandraceae family.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma; HBV, hepatitis B viruses; SC, Schisandra chinensis; Keap1/Nrf2/ARE, Kelch-like ECH-associating protein 1/nuclear factor erythroid 2 related factor 2/antioxidant response element; NF-κB, nuclear factor κB; TGF-β, transforming growth factor β; HIV, human immunodeficiency virus; APAP, Acetaminophen; t-BHP, tert-butyl hydroperoxide; CCl4, carbon tetrachloride; GalN, D-galactosamine; LPS, lipopolysaccharide; NAPQI, N-acetyl-p-benzoquinone imide; CYP2E1, cytochrome P450 enzyme, primarily cytochrome P450 2E1; GSH, Glutathione; ROS, reactive oxygen species; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MAPK, mitogen activated protein kinase; COX-2, cyclooxygenase-2; CYP, cytochrome P450; BCL-2, B-cell lymphoma-2; NADPH, nicotinamide adenine dinucleotide phosphate; LDH, lactate dehydrogenase; TNF-α, tumor necrosis factor-α; IL-6, interleukin 6; MDA, Malondialdehyde; SOD, superoxide dismutase; IL-10, interleukin-10; GPT, glutamic-pyruvic transaminase; WHO, World Health Organization; NAD+, nicotinamide adenine dinucleotide; KCs, Kupffer cells; JNK, c-Jun N-terminal kinase; HSCs, hepatic stellate cells; ER, endoplasmic reticulum; RIPK, receptor interacting protein kinase; MLKL, mixed lineage kinase domain like pseudokinase; PAMPs, pathogen-associated molecular patterns; PGE2, prostaglandin E2; NO, nitric oxide; INF-γ, interferon-γ; ERK 1/2, extracellular signal-regulated kinases 1 and 2; iNOS, inducible nitric oxide synthase; RIP2, receptor-interacting protein 2; log P, octanol-water partition coefficient.

* Correspondence to: TCM and Ethnomedicine Innovation & Development International Laboratory, School of Pharmacy, Hunan University of Chinese Medicine, Changsha, Hunan 410208, China.
E-mail address: wangwei402@hotmail.com (W. Wang).
[1] These authors contributed equally to this work.

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1. Introduction

The liver is a vital human organ responsible for metabolism, excretion, and detoxification. Due to the liver's considerable metabolic role, it is highly susceptible to disease. Liver injury can be caused by drugs [1–4], alcohol [5], and viruses [6,7]. The liver injury could be increasingly aggravated because of various factors and gradually convert into a vicious cycle of oxidative stress damage, inflammatory reaction and death of liver cells, eventually evolving into NAFLD, hepatic fibrosis or HCC [8]. NAFLD, hepatic fibrosis, and HCC are difficult to treat and prone to relapse [9]; therefore, it is crucial to treat early liver damage. Consequently, researchers are committed to find more effective drugs to treat liver injury.

The Schisandraceae family consists of climbing plants from the genera *Schisandra* and *Kadsura* with important economic and medicinal values. *Schisandra chinensis* (SC), a member of the Schisandraceae family, had been used to treat liver disease in China for centuries [10]. A follow-up study found SC extract effective in treating liver injury [11,12]. A special lignan which is high content in the Schisandraceae family is called dibenzocyclooctadiene lignan consisting of C-2/C-2' linkage and the usual C-8/C-8' juncture of the phenylpropanoid precursor units. It is mainly isolated from and is a characteristic compound of the Schisandraceae family. With researchers excavating dibenzocyclooctadiene lignans, and further studies found that it has liver protection anti-HIV, anti-tumor, and anti-oxidant activity [13]. Dibenzocyclooctadiene lignans play an outstanding role in liver protection. For example, Liu Gengtao conducted fruitful investigations on the pharmacology of SC, and found that the crude extract of SC and its various active components act on multiple targets and have the effects of liver protection, detoxification, antioxidant, promoting liver protein and glycogen synthesis, etc. Then schizandrin C, which belongs to dibenzocyclooctadiene lignans., was isolated. It was found that it had a good protective effect on liver injury caused by carbon tetrachloride (CCl_4) in mice [14]. On this basis, the structure of schizandrin C was modified, then two new drugs were obtained for hepatitis, Biphenyl Diester (DDB) and Bicyclol, were successfully studied in cooperation with colleagues [15,16]. After in-depth analysis and modification of biphenyls structure, a new compound, Bicyclol, was designed and synthesized successfully [17]. Its chemical structure is novel, bicyclol is safe and effective, easy to take orally, no accumulation in vivo, less adverse reactions, and low rebound rate [18]. It has obtained material invention patents from 15 countries including the United States, the European Union, Japan, and Korea, and is the first national class anti-hepatitis new drug with independent intellectual property rights in China. It was listed under the trade name Bicyclol Tablets in 2001. In addition, a large number of studies have shown that it has good therapeutic effects on liver damage caused by different substances [19–21]. These interesting therapeutic effects of dibenzocyclooctadiene lignans in vivo and in vitro have made researchers eager to further explore the medicinal properties of dibenzocyclooctadiene lignans from the Schisandraceae family.

This review collected the literature relevant to dibenzocyclooctadiene lignans using the keywords "dibenzocyclooctadiene lignans," "liver," "liver injury," and "Schisandraceae," in scientific databases "EBSCOhost," "PubMed," "Springer," "J-Stage," "ResearchGate," "ACS Publications" "ScienceDirect," and "Europe PMCl." This study covered dibenzocyclooctadiene lignans and bioactivity datum. Notably, statistical analysis of the distribution of dibenzocyclooctadiene lignans in different plants were effectively searched for specific molecules. In addition, the analysis of structure-activity relationships and absorption or permeation properties provided an important reference for structure-based drug design. This paper focused on comprehensively introducing the research progress of natural products, dibenzocyclooctadiene lignans to facilitate pharmacologists specialized in treating liver injury and pharmaceutical chemists in modifying highly active compounds.

2. Distribution and description of medicinal plants

Based on the Engler system, the Schisandraceae family is subdivided into two genera, *Schisandra* and *Kadsura*. The two genera comprise of about 50 species, widely distributed in East and Southeast Asia [22]. The collected literature suggested that dibenzocyclooctadiene lignans primarily exist in genera *Schisandra* (11 species) and *Kadsura* (13 species). The extent of dibenzocyclooctadiene lignans presence and the potency of the liver-protective effects vary among fruits, leaves, stems, and roots of the medicinal plants. Among them, stem and root content are more potent (Fig. 1).

Plants of the Schisandraceae family comprise of vines and wood and could be monoecious or dioecious. Leaves are simple and petiolate in conjunction with alternate or clustered. Flowers are axillary to the leaves on ultimate branches or in the axils of fugacious bracts near the base of ultimate shoots. They are generally solitary but occasionally in pairs or clusters of eight, unisexual, and hypogynous state, with a few to numerous parts generally spirally arranged, and pedunculate. Aggregates are gathered on unelongated receptacles to form globular aggregates or scattered on elongated receptacles to form spikelet aggregates. Seeds are mostly sparse but have rich endosperm and small embryos [23].

3. Phytochemistry

Dibenzocyclooctadiene lignans are special lignans, defined through their structure of C-2/C-2' linkage and the usual C-8/C-8' juncture of the phenylpropanoid precursor units. The dibenzocyclooctadiene lignans have a cyclooctadiene ring in their structure, consequently, the two benzene rings cannot rotate freely. This results in the difference between the two benzene rings and the cyclooctadiene ring structures in configuration, which is determined the absolute configuration of the biphenyl unit by CD spectrum. A dibenzocyclooctadiene lignan with an *R* configuration produces a CD spectrum with a negative Cotton effect at 220 nm and a positive Cotton effect at 254 nm [24]. Conversely, if the CD spectrum exhibits a positive Cotton effect at 220 nm and a negative Cotton effect at 254 nm, the biphenyl unit has the *S* configuration. At present, most of the isolated dibenzocyclooctadiene lignans are *S* configuration. In addition to the difference in configuration, the type, and location of substituents of dibenzocyclooctadiene lignans are also responsible for the high number of compounds. Methoxy and methylenedioxy groups are frequently reported substituents, while some other important substituents are acetyl, angeloyl, tigloyl, propanoyl, benzoyl, cinnamoyl, and butyryl groups [25]. Substituents like methoxy, hydroxyl, acetyl, angeloyl, tigloyl, propanoyl, benzoyl, isoval, isobut, methacrylate, phenyl, cinnamoyl, and butyryl are commonly present at C-1, C-6, C-9 and C-14. The Methylenedioxy group is mostly present at C-2/C-3 and C-12/C-13 (Fig. 2). For a cyclooctadiene ring, C-7 and C-8 is generally a substitution of methyl group, and the relative configuration of methyl groups is α. The C-7 and C-8 also have hydroxyl substitutions. The absolute configurations of C-7 and C-8 are both *S* and/or *R*. C-6 is usually replaced by an oxygenated β-substituent, and the absolute configuration is usually *R* in the absence of the C-7 hydroxyl group. C-9 is usually replaced by an oxygen-containing substituent of α, and the absolute configuration is generally *R*.

Currently, 358 compounds of dibenzocyclooctadiene lignans have been isolated and identified from the Schisandraceae family. The structural diversity of dibenzocyclooctadiene lignans lies in the differences between the substituents and relative and absolute configurations. Basesd on varying numbers of methylenedioxy group, ether formation in the ring and different configurations, dibenzocyclooctadiene lignans can be divided into with no methylenedioxy group, one methylenedioxy group, two methylenedioxy groups and other structures [26–134] (Figs. 2–3, Supplementary Figures 1–3, and Supplementary Tables 1–2).

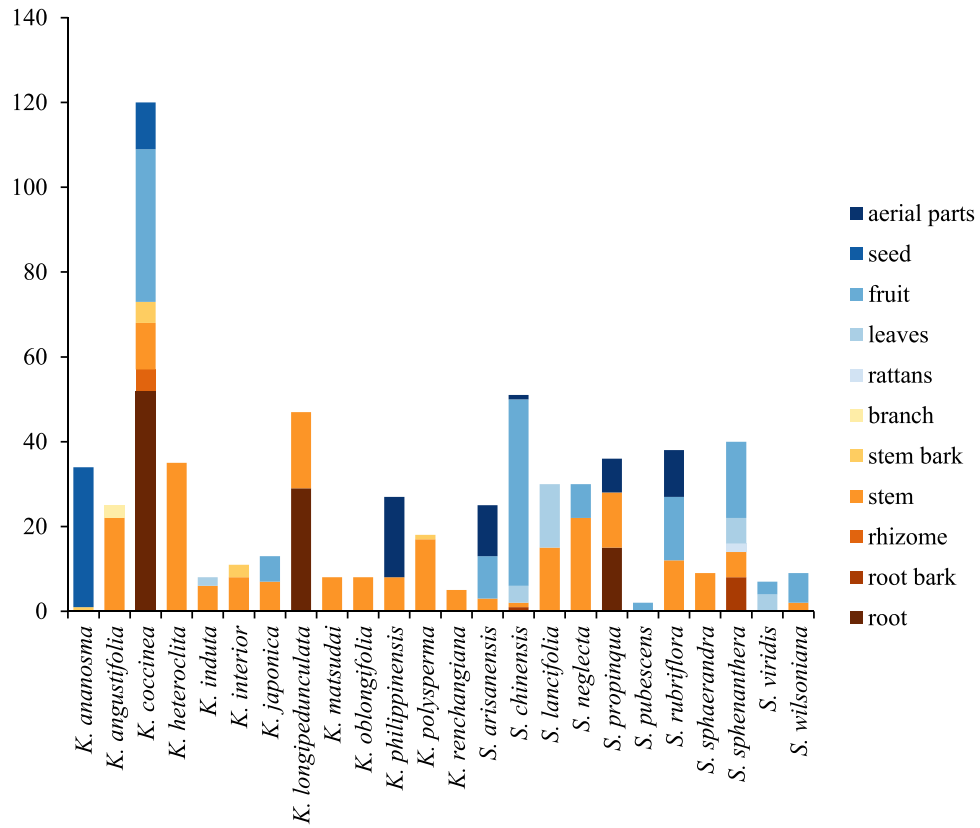


Fig. 1. Number of unique compounds isolated from different species that are members of the Schisandraceae family and different parts of the plant.

4. Protective effects on liver injury

Liver injury is caused by various factors, such as drugs, chemicals, alcohol and viruses. Many drugs cause hepatotoxicity, resulting in serious damage to hepatocytes. To take a classic example, acetaminophen (APAP) is a commonly used antipyretic pain reliever that is widely used in response to COVID-19. Excessive APAP can result in irreversible liver damage. Some chemicals, such as CCl_4, tert-butyl hydroperoxide (t-BHP), D-galactosamine (GalN)/lipopolysaccharide (LPS), and alcohol can also cause liver injury. Although the precise mechanisms vary, each agent led to liver damage by influencing oxidative stress. Dibenzocyclooctadiene lignans have been studied for liver injury caused by viruses. Furthermore, the pathophysiology of liver damage caused by viruses is intricate.

4.1. APAP

The reactive metabolite N-acetyl-p-benzoquinone imide (NAPQI) is produced as a result of APAP metabolism by the cytochrome P450 enzyme, primarily cytochrome P450 2E1 (CYP2E1) [135]. NAPQI is an extremely poisonous, highly reactive substance, detoxified by hepatic glutathione (GSH) into harmless mercapturic acid and cysteine derivatives and eliminated in the urine [2]. NAPQI, which is produced when APAP is ingested, depletes stored GSH. Without GSH, NAPQI covalently binds to cysteine groups on hepatocyte molecules to form NAPQI-protein adducts (so-called APAP-protein adducts) [136]. This is an irreversible process. Therefore, NAPQI induces oxidative stress via GSH depletion and reactive oxygen species (ROS) production, resulting in the death of liver cells [137,138].

At present, the ethanol extract of the stems of SC reduced aspartate aminotransferase (AST) and alanine aminotransferase (ALT), inhibiting Bax, mitogen-activated protein kinase (MAPK), and caspase-3, the expression levels of inducible nitric oxide synthase and cyclooxygenase-2 (COX-2) alleviating APAP-induced oxidative stress and inflammation by regulating MAPK and caspase-3 signaling pathways [11] (Fig. 4). The ethanol extract of *S. sphenanthera* prevented APAP-induced liver injury by inhibiting the bio-activation of APAP mediated by cytochrome p450, activating the Nrf2-antioxidant response element pathway to induce detoxification and antioxidation, regulating p53, p21, cyclin D1 and proliferating cell nuclear antigen, and promoting liver regeneration after APAP-induced liver injury [139] (Fig. 4). Compounds isolated from the Schisandraceae family have been screened for APAP liver injury in vitro (Table 1). For example, schizandrin (**80**) and gomisin M_2 (**285**) displayed liver protective activities against APAP-induced injuries in HepG-2 cells with survival rates of 44%, 43% and 44% at 10 μM [140]. Heilaohuguosus A (**154**) and L (**22**), kadsuphilol I (**25**), and tiegusanin I (**162**) displayed potential liver protective activity (survival rates: 53.5 ± 1.7%, 55.2 ± 1.2%, 52.5 ± 2.4%, and 54.0 ± 2.2%) against APAP-induced toxicity in HepG-2 cells at10 μM [28].

In addition to drug screening, it is also possible to further explore the potential pharmacodynamic mechanisms of compounds (Fig. 5). Deoxyschisandrin (**81**) displayed significant protective actions against APAP-induced liver injury through suppression of GSH depletion and partly through inhibition of cytochrome P450 (CYP)-mediated APAP metabolic activation [141]. Gomisin A (**251**) inhibited the elevation of serum aminotransferase activity, hepatic lipoperoxides content, and characteristic of APAP administration. It also reduced the appearance of histological changes such as degeneration and necrosis of hepatocytes [142]. In another study, schisandrol B (**251**) inhibited CYP-mediated APAP bio-activation and regulated the p53, p21, cyclin D1, proliferating cell nuclear antigen, and B-cell lymphoma-2 (BCL-2) and promoted liver regeneration [143]. Schisandrol A (**80**) resisted liver injury caused by excess APAP through regulating TNF signaling pathway, inhibiting oxidative stress, inflammatory response, and inhibiting CYP enzyme activity [144].

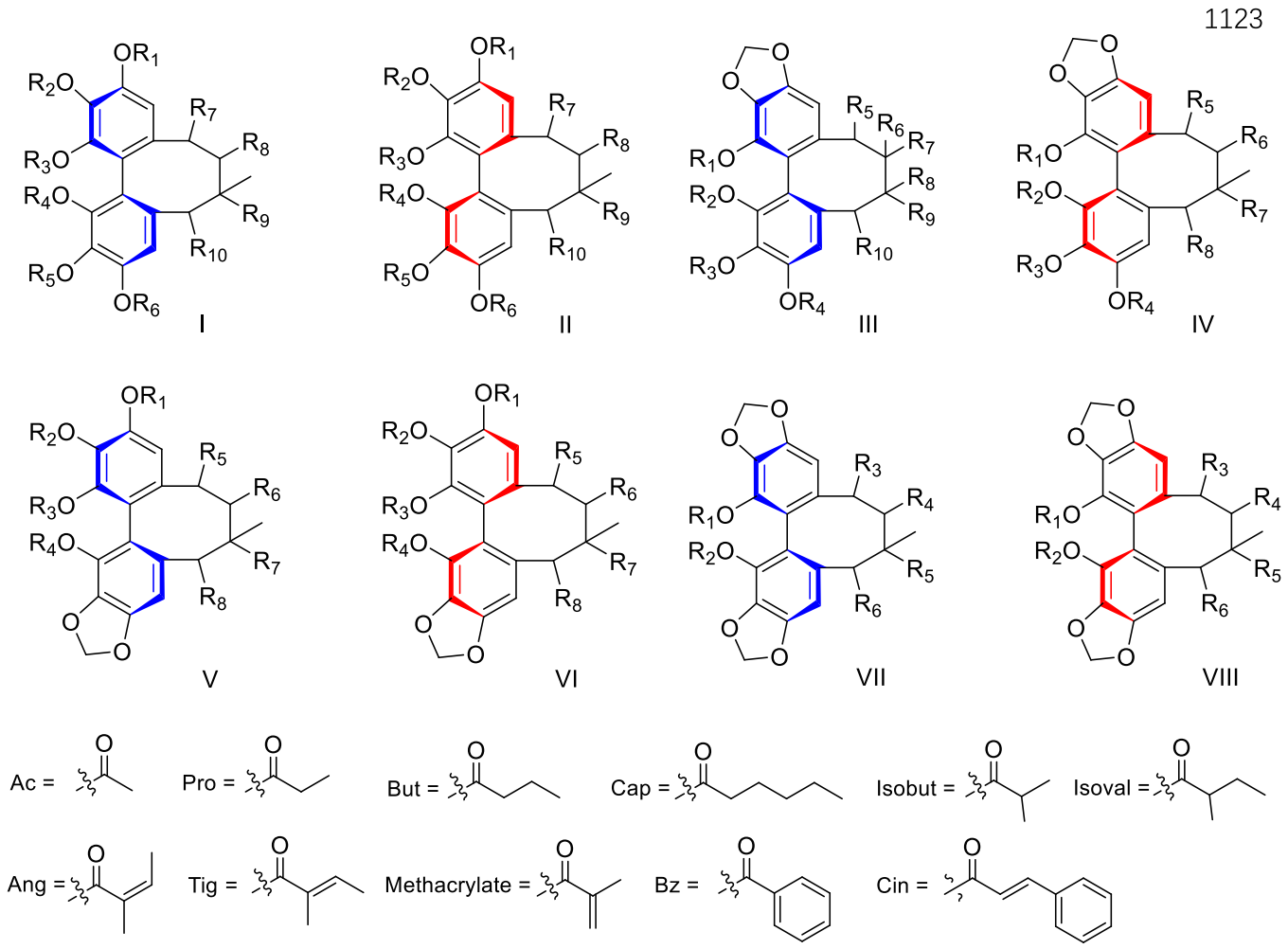


Fig. 2. The basic skeletons of dibenzocyclooctadiene lignans of the Schisandraceae family.

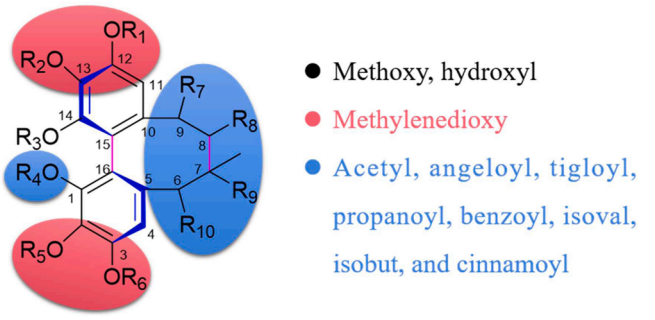


Fig. 3. The structure of dibenzocyclooctadiene lignans and other most commonly found substituents.

4.2. CCl_4

CCl_4 is a well-known hepatotoxin widely used to study the mechanism of acute and chronic hepatotoxicity in vivo [145,146]. It is also metabolized by CYP2E1, and the resultant free radical metabolites, including trichloromethyl and trichloromethyl peroxide, attack the cellular membrane, causing lipid peroxidation [147]. This oxidative stress induces liver cell death and, eventually severe necrosis around the central region of the liver [148].

The ethanol extract of *K. heteroclita* stems significantly reduces CCl_4-induced inflammatory cell infiltration, hepatic fibrosis, hepatocyte ballooning, necrosis and severe apoptosis of hepatocytes. Furthermore, it reduces the levels of ALT, AST, tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6). It also inhibits the production of malondialdehyde (MDA) and myeloperoxidase, and significantly increase the levels of superoxide dismutase (SOD) and interleukin 10 (IL-10) [149] (Fig. 4). The lignans containing extract from SC prevents CCl_4-induced liver injury by regulating NF-κB, JNK and Bcl-2/Bax signaling pathways to reduce inflammation and apoptosis [150] (Fig. 4).

As shown in Table 1, kadsurin (**120**), gomisin C (**215**), gomisin A (**251**), schisantherin D (**290**), and schisandrin C (**310**) displayed hepatoprotective effects against CCl_4-induced damage. Kadsurin (**120**) can lessen the CCl_4-induced lipid-peroxidation products [151]. Gomisin C (**215**) and schisantherin D (**290**) exhibited hepatoprotective properties against CCl_4-induced elevation of glutamic-pyruvic transaminase (GPT) levels [152]. Moreover, Schisandrin C (**321**) reduced GSH levels and GSH reductase activity [153]. Although gomisin A (**251**) and schisandrin C (**310**) exhibited no inhibition in CCl_3 radicals' formation, they inhibited CCl_4 enzymatic reaction with NADPH-CYP reductase and NADPH and non-enzymatic reaction without this system-induced lipid peroxidation [154]. Schisandrin B (**245**) cured hepatic toxicity by enhancing the redox status of mitochondrial GSH [155]. In addition to effectively relieving oxidative stress, schisandrin B (**245**) can also effectively treat inflammation and fibrosis by inhibiting macrophage polarization [156], on the other hand, inhibited kupffer cells (KCs) polarization by down-regulating NF-κB and p38 MAPK signaling pathways, targeting CB2 receptors [157].

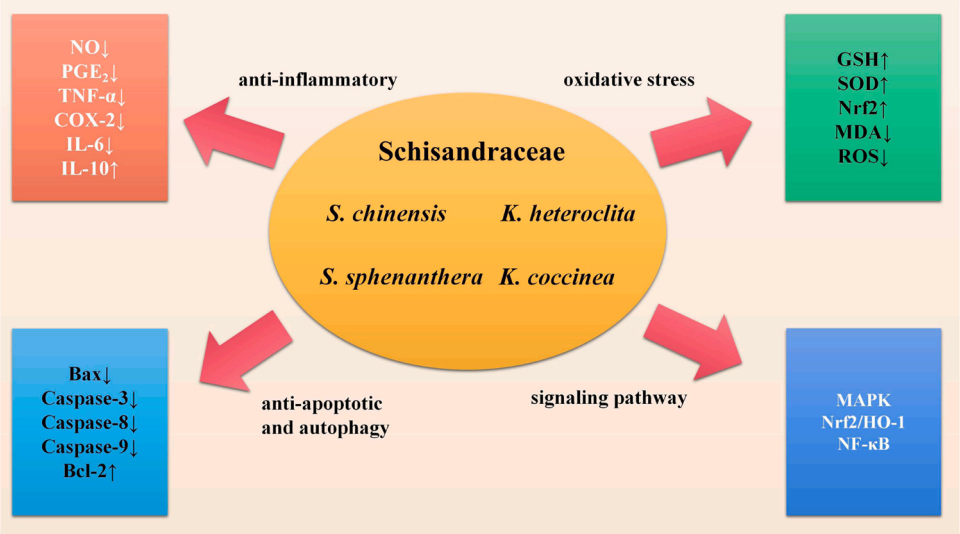


Fig. 4. Several methods of dibenzocyclooctadiene lignans to treat liver injury. Dibenzocyclooctadiene lignans treat liver injury by regulating the release of inflammatory factors, oxidative stress, autophagy, and several signaling pathways in the human body.

4.3. T-BHP

When metabolized by liver cells, t-BHP could easily induce lipid peroxidation in liver cells, leading to tissue peroxidation damage [158], which could be fatal to liver cells [159]. T-BHP reacts with GSH in the presence of GSH peroxidase to produce T-butanol and GSH disulfide [160,161]. GSH disulfide reduces to GSH using nicotinamide adenine dinucleotide phosphate (NADPH) as the energy source. Due to these two processes, the concentration of GSH and NADPH in cells changes. Consequently, this alters the existing Ca^{2+} state and causes its loss, resulting in the loss of cell viability [162].

Ban, N. et al. reported the antioxidant effect of dibenzocyclooctadiene lignans isolated from the roots of *K. coccinea* at the low t-BHP concentration (Table 1) [103]. It has been established that binankadsurin A (**133**), isovaleroylbinankadsurin A (**138**) and acetylepigomisin R (**302**) inhibit the peroxidation of t-BHP, but the specific mechanism of these two compounds has yet to be determined.

4.4. GalN /LPS

GalN is a hepatotoxic compound [163]. GalN decreases the concentration of cellular uridine-5'-triphosphate and reduces RNA synthesis in hepatocytes to avert hepatic transcription [164]. LPS induces cytokine release, producing cellular stress responses [165]. Previous studies have demonstrated the role of inflammatory response and oxidative stress in the LPS/GalN-induced pathological process [166,167].

Due to its high reproducibility and dose-controllability, GalN has been widely used in animal models for acute liver injury [168]. Based on these studies, GalN /LPS is often used to screen potential treatments for liver damage. As showed in Table 1, gomisin C (**215**) and schisantherin D (**290**) exhibited hepatoprotective properties against GalN-induced elevation of GPT levels [152] (Table 1). Gomisin A (**251**) protected against immunological liver injuries and reduced the mortality of the mice dose-dependently with LPS-induced acute hepatic failure [169], and the protective effects on hepatocyte apoptosis and liver failure induced by GalN and LPS were achieved by reducing oxidative stress and anti-apoptotic activity [170].

4.5. Alcohol

Alcoholic liver disease is likely to develop in individuals who consume 40 g of alcohol per day [171]. Furthermore, liver cells from ethanol-treated animals were more susceptible to the cytotoxic effects of cytokines than cells of control animals [5]. The hepatotoxicity of alcohol is principally the result of the acetaldehyde metabolism and stimulation of oxidative stress through alcohol dehydrogenase and CYP2E1 pathways [172]. Precisely, acetaldehyde converted from alcohol in vivo is toxic to hepatocytes, and the metabolic process of ethanol production of acetaldehyde consumes nicotinamide adenine dinucleotide (NAD^+), resulting in the NAD^+/NADH redox ratio reduction and mitochondrial damage [173]. Increasing acetaldehyde concentration also contributes to rising ROS production, and ethanol can interact with membrane phospholipids, stimulate KCs, mobilize iron, decrease antioxidants, and increase oxidative stress [174].

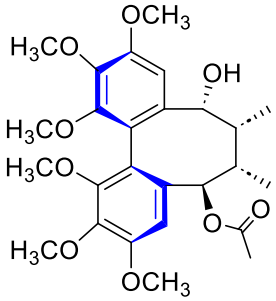
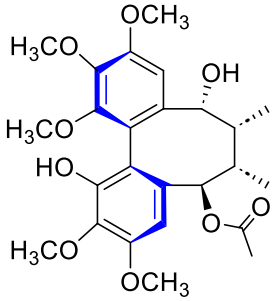
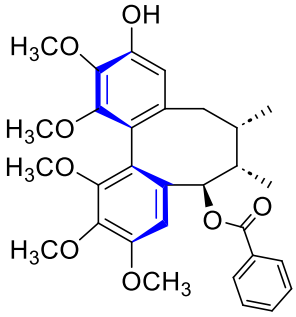
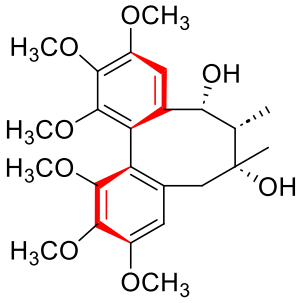
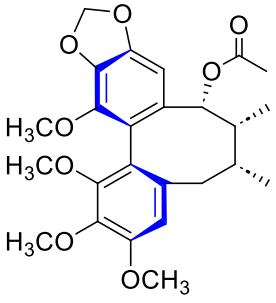
The SC extract significantly repressed six liver P450s of rat liver microsomes in vitro and alcohol metabolism, reducing the alcohol-induced liver damage [175] (Fig. 4). Schisantherin A (**215**) inhibited alcohol-induced oxidative stress and liver inflammation in a dose-dependent manner [176]. The pathway and mechanism of gomisin N (**217**) for the treatment of alcoholic liver disease are complicated, mainly by inhibiting hepatic steatosis, oxidative stress and inflammation [177].

4.6. Human hepatitis viruses

Among seven human hepatitis viruses (A-E, G and TT virus), the chronic infection is principally contributed by the HBV, which can persist in the host for years [6]. HBV causes liver cell injury primarily through the oxidative stress response and by stimulating an excessive immune response [7,178,179]. During persistent infection, liver inflammation maintains the cycles of liver cell destruction and regeneration, forming the pathogenic basis of chronic hepatitis and resulting in hepatic fibrosis, cirrhosis and HCC [6].

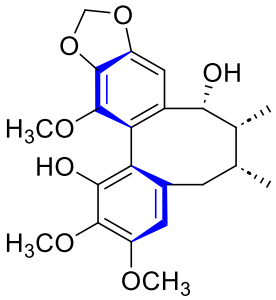
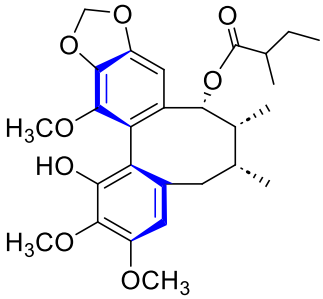
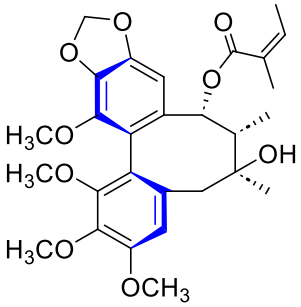
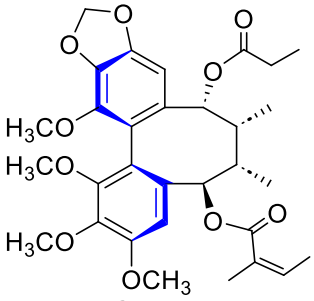
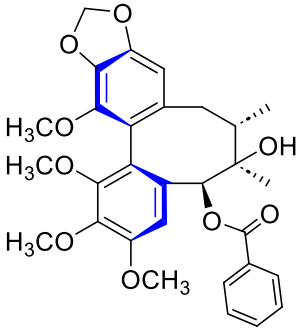
As shown in Table 1, kadsurindutin A (**304**), kadsulignan L (**351**), schinlignan G (**91**) and methylgomisin O (**219**) displayed anti-HBV activity. Kadsurindutin A (**304**) and kadsulignan L (**351**) exhibited moderate antiviral activities [128]. Schinlignan G (**91**) and methylgomisin O (**219**) shown potent anti-HBV activity against HBV DNA replication with

Table 1
Summary of the hepatoprotective activity of dibenzocyclooctadiene lignans from the Schisandraceae family.

NO.	Compounds	structures	Activities	References
22	heilaohuguosu L		APAP-induced HepG-2 cells survival rates↑ (55.2 ± 1.2%, 10 μM)	[28]
25	kadsuphilol I		APAP-induced HepG-2 cells survival rates↑ (54.0 ± 2.2%, 10 μM)	[28]
70	benzoylgomisin U		HSC-T6 cell proliferation↓(50 μg/ml)	[68]
80	schizandrin		APAP-induced HepG-2 cells survival rates↑ (44%, 10 μM)	[140]
120	Kadsurin		CCl_4-induced SOD↑	[151]

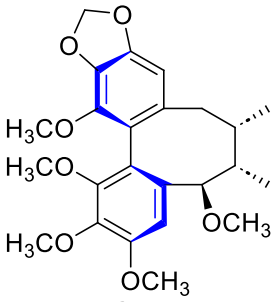
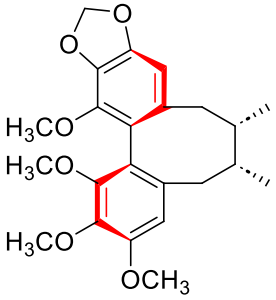
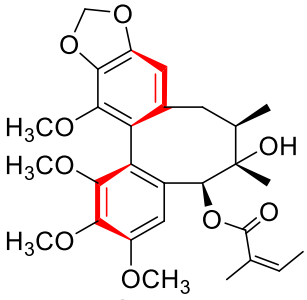
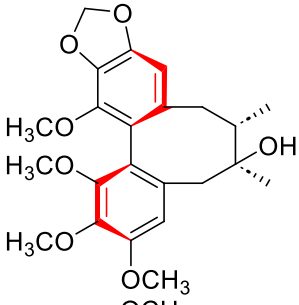
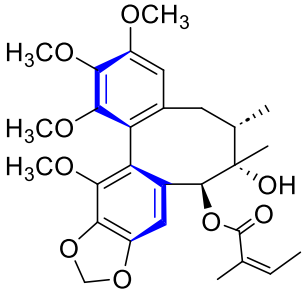
(*continued on next page*)

Table 1 (*continued*)

NO.	Compounds	structures	Activities	References
133	binankadsurin A		1.2 mM tBH-induced LDH leakage↓ (ED_{50}: 79.3 μM)	[103]
138	isovaleroylbinankadsurin A		1.2 mM tBH-induced LDH leakage↓ (ED50: 26.1 μM)	[103]
154	heilaohuguosu A		APAP-induced HepG-2 cells survival rates↑ (53.5 ± 1.7%, 10 μM)	[28]
162	tiegusanin I		APAP-induced HepG-2 cells survival rates↑ (52.5 ± 2.4%)	[28]
215	gomisin C		GaIN-induced GPT↓	[152]

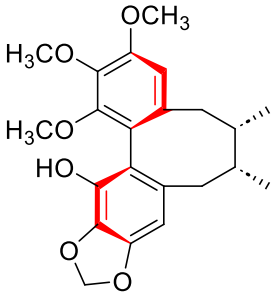
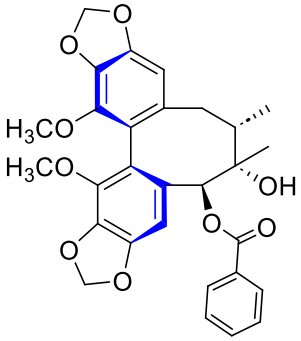
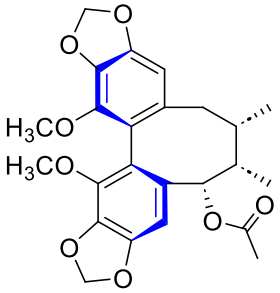
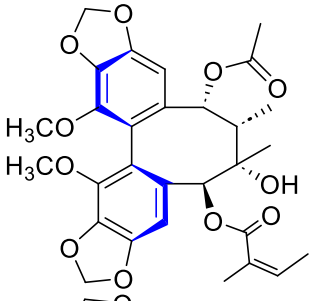
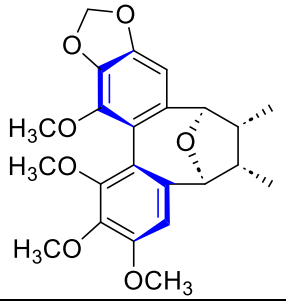
(*continued on next page*)

Table 1 (*continued*)

NO.	Compounds	structures	Activities	References
219	methylgomisin O		HBV DNA replication↓in the HepG2 2.2.15 cell line	[56]
245	schisandrin B		the redox status of mitochondrial GSH↑	[155]
260	schisphenin D		HSC-T6 cell proliferation↓ (50 μg/ml)	[68]
251	gomisin A		LPS-induced Mouse mortalitys↓	[169]
262	gomisin F		HSC-T6 cell proliferation↓(50 μg/ml)	[68]

(*continued on next page*)

Table 1 (*continued*)

NO.	Compounds	structures	Activities	References
285	gomisin M_2		APAP-induced HepG-2 cells survival rates↑ (43%, 10 μM)	[140]
290	schisantherin D		$CC1_4$ GaIN-induced GPT↓	[152]
302	acetylepigomisin R		1.2 mM tBH-induced LDH leakage↓ (ED50: 135.7 μM)	[103]
304	kadsurindutin A		human hepatitis B and E antigen-effects↑in the HepG2 2.2.15 cell line (0.2 mg/ml)	[128]
351	kadsulignan L		inhibiting human hepatitis B and E antigen secretions↑ in the HepG2 2.2.15 cell line (0.1 mg/ml)	[128]

IC_{50} values of 5.13 and 5.49 μg ml^{-1}, respectively [56].

5. The main mechanisms related to liver injury

5.1. Oxidative stress

Oxidative stress is a common mechanism of liver injury. When drugs, chemicals, and alcohol are metabolized by liver cells, large amounts of ROS are produced, disrupting the equilibrium between the oxidative and antioxidant systems. Excessive ROS causes irreversible oxidation of proteins, lipids, and nucleic acids, involving multiple target organelles, including mitochondria, Golgi apparatus, endoplasmic reticulum, and other organelles, thereby affecting cell proliferation and instigating cell injury and death. The MAPK extracellular signal-regulated kinase 1/2, c-

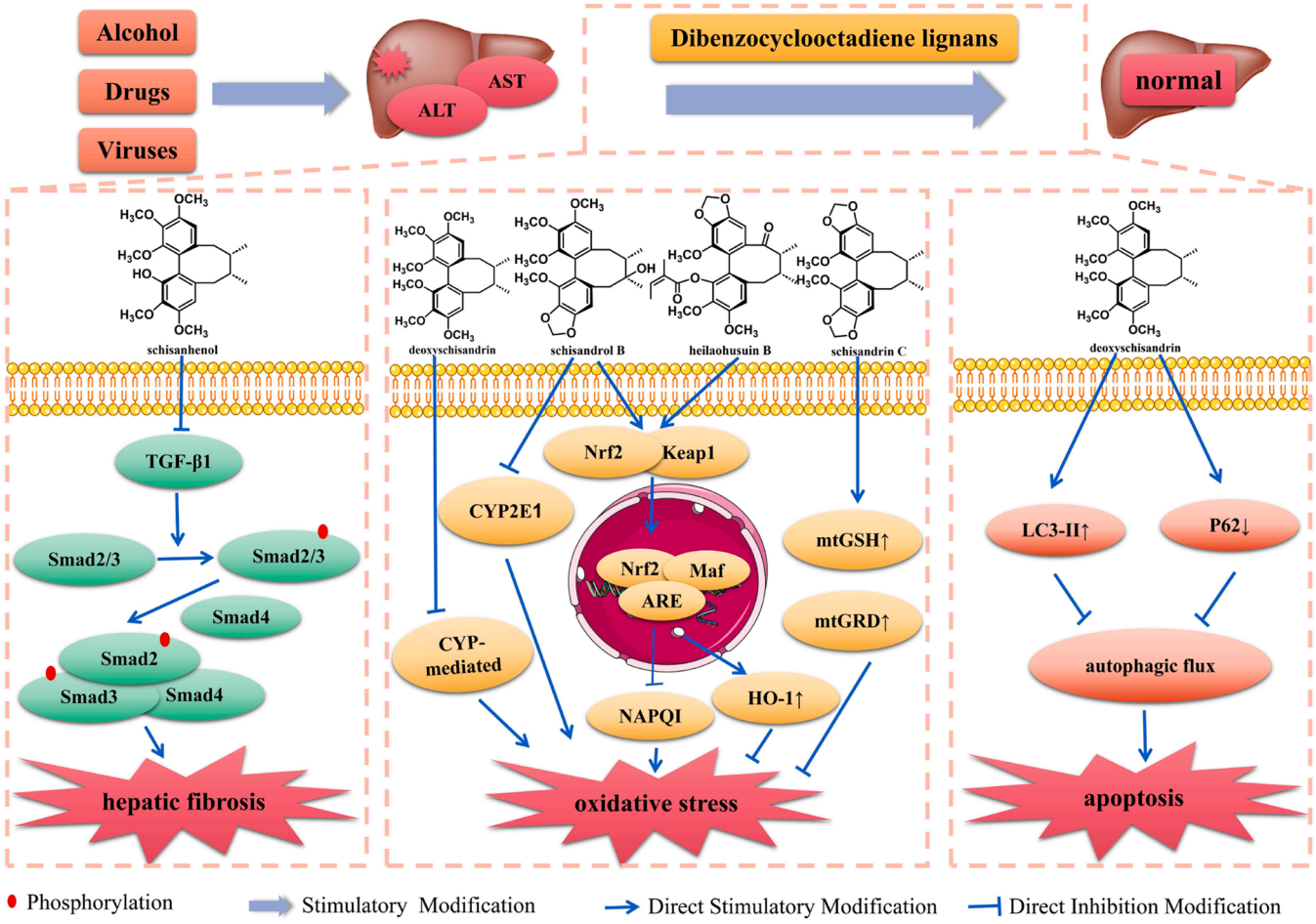


Fig. 5. The signaling pathway of the effective ingredients from the Schisandraceae family in treating the liver injury.

Jun N-terminal kinase (JNK), and Keap1/Nrf2/ARE pathways which are regulatory pathways of hepatocyte oxidant injury [180].

SC seed lignans extract mainly included schizandrol A (**80**), schisandrin A(**81**), schisandrin B (**245**), and schisandrol B (**251**) by using HPLC analysis, and could dose-dependently alter serum and liver lipid profiles, by maintaining normal serum transaminase activity and reduce liver lipid peroxidation in alcohol-induced mice [181] (Fig. 4). Su, L. et al. determined the main chemical constituents of the ethanol extract of the SC were gomisin J (**15**), schizandrin (**80**), deoxyschisandrin (**81**), schisandrin B (**245**), gomisin G (**270**), and schisandrin C (**310**) by HPLC/UV detector [182]. And the further experimental proof that the inhibitory effects of the ethanol extract of the SC on alcohol-induced liver injury is related to its inhibition of CYP2E1 activation and activation of the Nrf2/ARE signaling pathway [182] (Fig. 4).

Oxidative stress is the most prevalent cause of liver damage. Thus, researchers have investigated the effects of lignans on oxidative stress (Fig. 5). Heilaohusuin B (**337**) increased Nrf2 expression [73]. Schisandrol B (**251**) exhibited a remarkable protective effect against APAP-induced hepatotoxicity, partially via activation of the Nrf2/ARE pathway and regulation of Nrf2 target genes, inducing detoxification and increasing antioxidant capacity [183]. Gomisin J (**15**) inhibited lipid peroxidation of rat liver corpuscle membrane and had inhibitory action on both Fe^{2+}/ascorbic acid and NADP/NADPH-initiated lipid peroxidation in rat liver mitochondria [184]. Angeloylgomisin H (**84**) and gomisin G (**270**) had DCFH-DA cellular-based activity, with IC_{50} values of 38.2 and 81.5 μM, respectively. It is interesting to note that the antioxidant activities of schisandrene (**345**) are comparable to the commercial antioxidant vitamin C and trolox [87]. Kadsuphilol C (**316**) exhibited more potent activity than vitamins C and E [86]. Angeloylbinankadsurin A (**141**), kadsuphilin A (**147**), and schizanrin J (**174**) have weak antioxidant activities [48].

5.2. *Inflammation*

Inflammation is the body's first line of defense against risk factors such as viruses, alcohol, and fat. However, excessive inflammation can exacerbate liver damage brought on by risk factors. These risk factors induce oxidative stress, and the ROS produced by oxidative stress can promote hepatocyte apoptosis, leading to liver injury and hepatic stellate cells (HSCs) [185]. Parenchymal damage, increased by apoptotic bodies, KCs activation, oxidative species production, and extracellular matrix remodeling, is a common consequence of liver injury [186]. HSCs receives a wide array of signals from damaged/dead liver and immune cells, primarily KCs. Factor-β1, a transforming growth factor (TGF) derived from KCs, activates HSCs and is the most potent fibrotic agonist. Furthermore, KCs promotes liver fibrosis by promoting the survival of activated HSCs in an NF-κB-dependent manner. It has been demonstrated that the crosstalk between KCs and HSCs is mediated by inflammatory cytokines: IL-1β and TNF-α [187]. Current researches focus on apoptosis recognized relatively easily due to its unique morphology, but cell death may occur in the form of necroptosis and pyroptosis [188]. Most of the studies of necroptosis involve the TNF signaling pathway [189]. After TNF ligation, the formation of "necrosome" occurs where receptor interacting protein kinase 1 (RIPK1) and RIPK3 undergo trans- and autophosphorylation [190]. After phosphorylation of mixed lineage kinase domain like pseudokinase (MLKL) by RIPK3, p-MLKL undergoes a conformational change and oligomerizes, binding to lipids in the plasma membrane, that is sufficient to execute cell lysis [188]. As for pyroptosis,

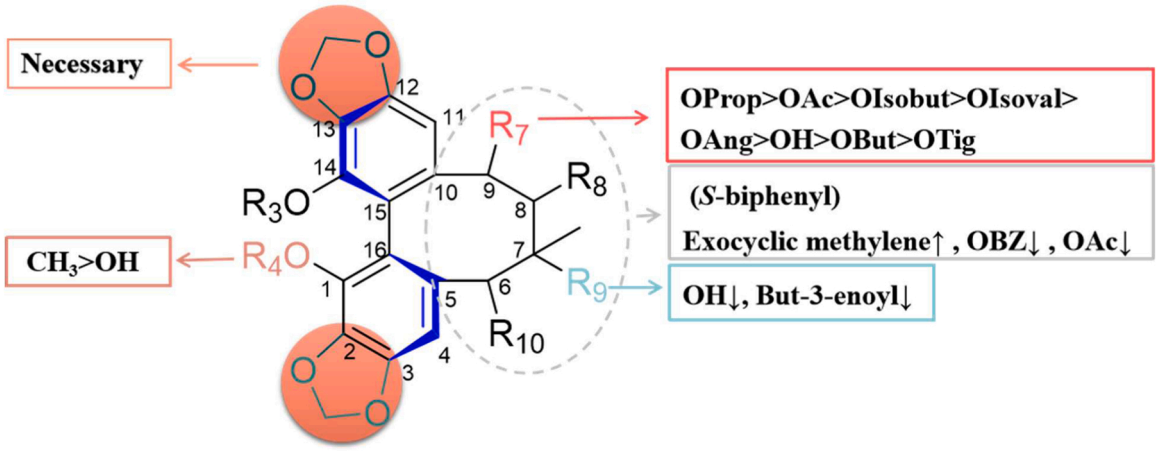


Fig. 6. The potential structure-activity relationships of dibenzocyclooctadiene lignans.

it occurs primarily in response to intracellular pathogens or pathogen-associated molecular patterns (PAMPs) [188]. At present, Dibenzocyclooctadiene lignans is mainly about apoptosis and its macroscopic manifestations, and there are few studies on necroptosis and pyroptosis.

Through suppressing NF-κB activity, water extract from SC fruits downregulated the expression of pro-inflammatory genes involved in the synthesis of nitric oxide (NO), prostaglandin E_2 (PGE_2), and TNF-α in LPS-stimulated RAW 264.7 macrophage cells [191] (Fig. 4). The lignans of SC inhibited inflammation in RAW 264.7 macrophages stimulated by LPS [192]. Leaves extract of *K. coccinea* inhibited the secretion of NO, reduced the level of COX-2 in the protein, inhibited the secretion of pro-inflammatory cytokines IL-6, and promoted the secretion of anti-inflammatory cytokine IL-10, showing a good anti-inflammatory effect [193]. The dried fruit of SC regulates the LPS-induced NF-κB-dependent inflammatory pathway mainly by inhibiting the activation of MAPKs [194] (Fig. 4). As shown in Fig. 5, schisanhenol (**85**) displayed activity by inhibiting the TGF-β/Smad and MAPK signaling pathways [195]. Schisantherin D (**290**) affected endothelin B receptor, fibrosis and antioxidant-related proteins (e.g., p-Smad2/3, Nrf2, and Smad7), showed association with modulating endothelin B receptor-linked fibrosis and anti-oxidative related signaling [196]. Benzoylgomisin U (**70**), schisphenin D (**260**) and gomisin F (**262**) displayed hepatoprotective activities against damage in HSCs [68]. Schisandrol B (**251**) inhibited activation of NF-κB, leading to the down-regulation of pro-inflammatory mediators and amelioration of fibrogenesis [197]. Schisphenin A (**67**), gomisin K_3 (**82**), schisantherin D (**290**) have been reported with obvious anti-hepatic fibrosis activities [67]. Schisantherin A (**215**) and methylgomisin O (**219**) showed significant inhibitory activities against TNF-α and IL-6 [113]. Kadsuralignan J (**139**) showed inhibitory activity on NO production by the murine macrophage-like cell RAW264.7, which was activated by LPS and recombinant mouse interferon-γ (INF-γ) [105]. Gomisin J (**15**), gomisin N (**217**), and schisandrin C (**310**), showed hepatoprotective activities to reduce NO production from LPS-stimulated Raw 264.7 cells through blockage of MAPK, extracellular signal-regulated kinases 1 and 2 (ERK 1/2), and JNK phosphorylation [198]. Schisandrin B (**245**) prevented the progression of liver fibrosis by regulating Nrf2/ARE and TGF-β/Smad signaling pathways [199]. Schisantherin A (**215**) inhibited the production of LPS-induced inflammatory cytokines by blocking NF-κB and MAPK signaling pathways in RAW 264.7 cells [200]. Schisandrin A (**81**) protected against LPS-induced inflammation and oxidation in RAW 264.7 cells primarily by inhibiting NF-κB, MAPK pathways, and partly by Nrf2/HO-1 pathways [201]. The anti-inflammatory effects of gomisin A (**251**) may be through down-regulating the activation of receptor-interacting protein 2 (RIP2) and NF-κB to inhibit the expression of COX-2, inducible nitric oxide synthase (iNOS), IL-6, TNF-α and NO [202].

5.3. Autophagy

Autophagy, a cellular catabolic process mediated by lysosomes, plays an important role in maintaining cellular and metabolic homeostasis in the liver [203]. Several liver illnesses, including alcohol-related liver disease, NAFLD, drug-induced liver damage, viral hepatitis, and HCC, are reported to be involved in autophagy dysfunction or dysregulation [203]. Autophagy is a stress response activated by physical stress [204]. Cumulative evidence indicates that endoplasmic reticulum stress and ROS from mitochondrial damage can trigger autophagy [205]. Autophagy has a dual role in body regulation. It serves as a survival mechanism and a trigger for autophagy death in certain circumstances [206]. Many protein complexes, including the mammalian target of rapamycin complex 1, the UNC-51-like kinase 1 complex, and the Beclin1 complex, are involved in the start of autophagy and the early assembly of autophagosomes [207]. Over 40 autophagy-related genes are associated with the multistep autophagy process that causes catastrophic liver damage [203]. Currently, there are some studies related to effects of lignans on autophagy. As shown in Fig. 5, schisandrin A (**81**) activated autophagy flux and inhibited apoptosis [208]. Gomisin N (**217**) activates mTOR and inhibits ULK1 (the negative downstream effector of mTOR) activity, thus inhibiting autophagy [209].

6. Structure-activity relationship of dibenzocyclooctadiene lignans

In most of the cases, substituents like methoxy, hydroxyl, acetyl, angeloyl, tigloyl, propanoyl, benzoyl, isoval, isobut, methacrylate, phenyl, cinnamoyl, and butyryl are present at C-1, C-6, C-9 and C-14. The Methylenedioxy group is mostly present at C-2/C-3 and C-12/C-13. Two benzene rings and the substituents in the structure effectively resist oxidation. Moreover, the degree of liver protection provided by various substituents varies [210]. Many researchers reported that substituents play an important role in anti-oxidative stress (Fig. 6).

Recent research has centered on the crucial role of the methylenedioxy group in antioxidation. In the experiment of dibenzocyclooctadiene lignans on reducing CCl_4-induced cell damage, dibenzocyclooctadiene lignans containing methylene glycol increased the level of GSH in the liver mitochondria of mice, thereby protecting the mice from CCl_4 hepatotoxicity [210]. The methylenedioxy group of dibenzocyclooctadiene lignans is an important structural determinant of

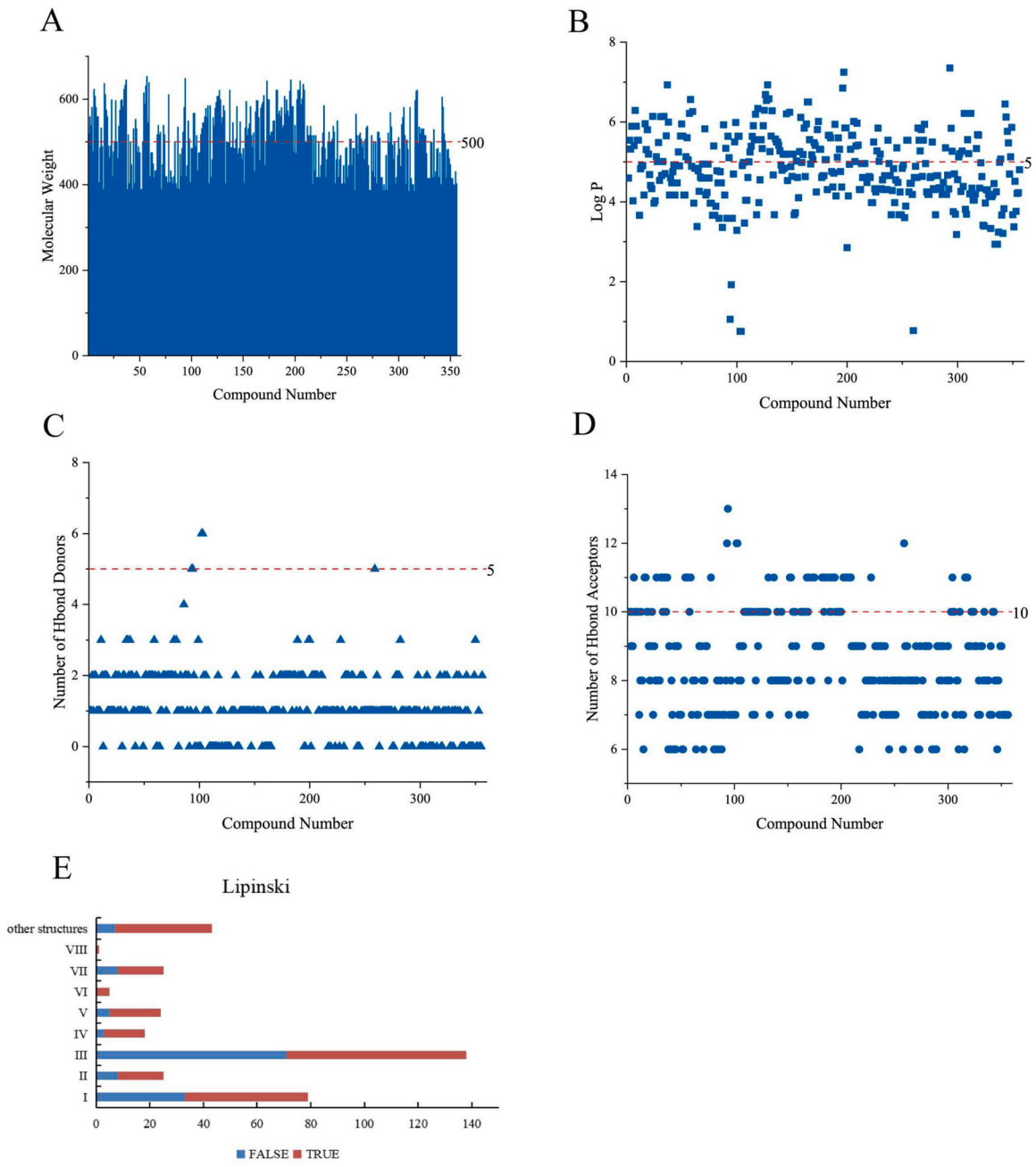


Fig. 7. Analysis of absorption or permeation properties of 358 compounds of dibenzocyclooctadiene lignans from the family Schisandraceae based on Lipinski's rule of five. (A) Molecular weight; (B) octanol–water partition coefficient [log P]; (C) number of hydrogen bond donors; (D) number of hydrogen bond acceptors; (E) the ratio of the number of compounds with and without absorption or permeation properties of different skeletons.

mitochondrial GSH-stimulating activity. Siu-po IP et al. studied the effects of schisandrin A (**81**) and schisandrin C (**310**) on the liver mitochondria of mice exposed to CCl_4 [153]. It was found that the methylenedioxy and cyclodiene of dibenzocyclooctadiene lignans played an important role in promoting the antioxidant effect of hepatic mitochondrial GSH.

In addition to the methylenedioxy group, other substituents can strengthen or weaken the bioactivities of lignans. The methylenedioxy group is essential for the antioxidant activity of *S*-biphenyl, as the benzoyloxy group probably enhances such effects [87]. The 6, 9-oxygen bridge unit and a keto group at C-9 are unnecessary for the activity, and in the case where the substituents at other positions are the same, these compounds with different oxygen-containing substituents at C-9 in cyclooctadiene ring have varying protective effects [73]. There is a novel finding that dibenzocyclooctadiene lignans, which have *S*-biphenyl and methylenedioxy groups, strongly inhibited LPS-induced microglial activation. The methoxy group on the cyclooctadiene is more effective, while an acetyl group on the cyclooctadiene or hydroxyl group on C-7 decreased the inhibitory activity [111].

In addition, the methylenedioxy group increases anti-HBV activity, whereas the C-9 hydroxyl weakens or even nullifies the effect [49]. The lignan with a But-3-enoyl group exhibited inhibitory activity against human hepatitis B and E antigens [211], suggesting that this structure in dibenzocyclooctadiene lignans plays a role against HBV.

7. The absorption or permeation properties of the dibenzocyclooctadiene lignans

In general, the drug properties of chemical molecules can be preliminarily determined according to Lipinski's rule of V [212–214]. Lipinski's rule V is that molecular mass no more than 500 Dalton, octanol-water partition coefficient [log P] not exceed 5, hydrogen bond acceptors no more than 10, hydrogen bond donors no more than 5 [215]. Our search and interpretation of literature suggested that among the 358 compounds, 163 compounds had molecular weights no more than 500 (Fig. 7A). log P values of 211 compounds not exceed 5 (Fig. 7B). 356 compounds had not exceeded 5 hydrogen bond donors (Fig. 7C); The number of hydrogen bond acceptors in 307 compounds was no more than 10 (Fig. 7D). Overall, 223 compounds, or 62%, met all the criteria for Lipinski's five rules; just remaining 135 compounds (38%) did not pass the Lipinski rule (Supplementary Table 3). Compounds of different skeleton types have different absorption or permeation properties, with the third group having more compounds but the proportion of compounds with poor adsorption or permeability is larger. (Fig. 7E). Although the extracts from the family Schisandraceae can effectively inhibit liver damage, further research is needed to determine which compounds have the potential to be developed into drugs.

8. Conclusions and perspectives

Lignans are prevalent in the natural world. Dibenzocyclooctadiene lignans have a special structure and potential for liver protective activity and are mainly isolated from plants. These are the characteristic compounds of the Schisandraceae family. This review discussed the major activities of dibenzocyclooctadiene lignans reported until the end of 2022 from Schisandraceae family, including distribution resources, absorption or permeation properties, hepatoprotective activities, and structural-activity relationships.

In this review, 358 dibenzocyclooctadiene lignans were assessed and classified into nine classes based on their relative configuration and the number of methylenedioxy moieties. According to our findings, among 358 dibenzocyclooctadiene lignans, the absolute configuration was *S*, and the number of its compounds containing methylenedioxy was the largest. Electron-donating substituents, such as hydroxyl, methoxy, and methylenedioxy, were found in benzene rings and C-6, C-7, C-8, and C-9. The electron-withdrawing substituents were mainly attached at C-1, C-6, C-9, and C-14. In most cases an ether bond between C-7 and C-8 was observed.

Furthermore, among 358 dibenzocyclooctadiene lignans, 37 compounds were with hepatoprotective activities. In addition to the basic study on the drug efficacy of a single compound, there are also pharmacological activities of different extracts and fractions from the Schisandraceae family. The results demonstrated that the pharmacological activities of lignans rich extracts were significantly higher than other extracts. In addition, qualitative and quantitative analyses of the extracts further revealed that compounds with liver protective activity are regulated primarily by oxidative stress, inflammation, and autophagy. These compounds can up-regulate antioxidant levels, such as SOD, GSH, and Nrf2, and down-regulate the levels of MDA, ROS, AST, and ALT, through activation of antioxidant pathways, such as MAPK, Keap1/Nrf2/ARE, and JNK. Regarding anti-inflammatory effects, these lignans down-regulates inflammatory cytokines: TNF-α, IL-6, and COX-2, and up-regulates anti-inflammatory cytokines, IL-10 via participating in the NF-κB, TGF-β/Smad and other related inflammatory signaling pathways. In terms of anti-autophagy and apoptosis, they up-regulates anti-apoptotic factors, Bcl-2 and down-regulates pro-apoptotic factors such as Bax and caspase-3 through Bcl-2/Bax and casp enzyme-related pathways.

Simultaneously, the different activities of various dibenzocyclooctadiene lignans provided an important reference for the rapid screening of compounds. The structure activity relationship of dibenzocyclooctadiene lignans indicated that its bioactivity is closely related to its substituents. The methylenedioxy and *S*-biphenyl groups are mainly responsible for increase in their bioactivities, while presence of some groups, such as an acetyl group on the cyclooctadiene or hydroxyl group on C-7 decreases the bioactivities. On the basis of these structure-activity relationships, compounds with higher liver protective activities can be explored through structural modifications.

Although substantial progress has been made in all areas of dibenzocyclooctadiene lignan research, there were still some limitations.: (1) Despite some scientists having isolated dibenzocyclooctadiene lignans, their pharmacological properties have not been thoroughly investigated. Therefore, the effects of substituent type, orientation, spatial location, and *S* and *R* configuration in dibenzocyclooctadiene lignans could not be explained effectively. (2) Only 24 of the 50 species of the family Schisandraceae were explored. The unstudied plants from this family may be a potential treasure trove of chemically diverse dibenzocyclooctadiene lignans waiting to be discovered. This paper aimed to establish a comprehensive knowledge of dibenzocyclooctadiene lignans in the Schisandraceae family and to serve as a useful reference for the modern research of these compounds.

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CRediT authorship contribution statement

Shi-qi Liu and Yu-pei Yang wrote and revised the manuscript. Nusrat Hussain, Yu-qing Jian, Bin Li, Yi-xing Qiu, Huang-he Yu, and Hui-zhen Wang helped with the literature search and correction of the manuscript. Wei Wang provided the conception and design of the review, and directed the writing of the manuscript.

Declaration of Competing Interest

On behalf of, and having obtained permission from all the authors, I declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled. I testify to the accuracy of the above on behalf of all the authors.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2023.106872.

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