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Functional food potential of *Cornus officinalis* for liver health: mechanistic evidence and perspectives

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ABSTRACT

Liver diseases remain a global health crisis, with limited safe therapeutic options. *Cornus officinalis*, a traditional medicinal-edible plant, has demonstrated significant hepatoprotective potential. This review systematically summarizes its liver-protective mechanisms and explores its potential as a functional food. Data were collected from scientific databases such as PubMed, ScienceDirect, Elsevier, Google Scholar, and relevant literature. Key bioactive compounds—including iridoids, polyphenols, and polysaccharides—contribute to hepatoprotection by mitigating oxidative stress, inflammation, steatosis, apoptosis, and by regulating gut microbiota. As critical quality markers, iridoids exhibit suboptimal bioavailability, necessitating targeted technological interventions—nanoencapsulation for liver-specific delivery and microbial fermentation for controlled aglycone conversion are proposed to enhance their pharmacokinetic properties and bioactivity. Future research could adopt encapsulation and fermentation technologies for *C. officinalis* processing, aiming to develop targeted functional food products with enhanced bioactivity of its active components. This review, for the first time, establishes a "component-pathway-integration" model, providing a theoretical framework for evidence-based CO-derived functional food development and highlighting the need for further research on iridoid metabolic transformation to advance liver health management.

1. Introduction

Liver disease continues to be a significant global health concern, and there is still a scarcity of safe and effective treatments[1]. Each year, approximately 2 million individuals worldwide succumb to liver disease, as indicated by statistics[2]. The high mortality rate is closely related to the rising burden of diseases such as viral infection[3], excessive drinking[4], obesity[5] and drug abuse[6]. There are potential adverse effects associated with contemporary interventions, such as liver transplantation and hepatoprotective agents, which are effective for specific liver conditions. Furthermore, liver diseases' insidious progression and protracted latency impede their early detection and intervention[7]. Consequently, the identification of safe and effective natural therapies for the prevention and management of liver disease has emerged as a critical research priority. Consequently, the identification of safe and effective natural therapies for the prevention and management of liver disease has emerged as a critical research priority.

Cornus officinalis Sieb. et Zucc. is widely distributed across Eastern Europe and Asia[8]. It has attracted growing scientific interest as a functional food due to its rich bioactive constituents, including iridoid glycosides, polyphenols, polysaccharides, and organic acids[9-11]. Among these, iridoid glycosides are the most abundant and pharmacologically distinctive components. As a traditional Chinese medicine, *C. officinalis* is categorized as a "superior grade" herb in *Shennong's Classic of Materia Medica*. It has slightly warm properties, a sour-astringent flavor, and tropism for the liver and kidney meridians, with effects of tonifying the

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liver and kidneys and inducing astringency[12]. It is also a key ingredient in classic herbal formulations such as *Liuwei Dihuang Wan* and *Zuogui Wan*, which are used for liver and kidney regulation and protection. Modern pharmacological studies have shown that *C. officinalis*' active components exert diverse bioactivities, notably hepatoprotection[13-15], improvement of diabetes mellitus and its complications[16-17], anti-inflammation[18-19], neuroprotection[20], nephroprotection[21], immunomodulation[22], antioxidant[23-24], antibacterial[25], and osteoporosis prevention[26-27]. Currently, European cornelian cherry (*Cornus mas*, CM) fruits are predominantly applied in the production of food products such as fruit juice, jam[28], and fruit vinegar[13]. In 2023, China officially listed *C. officinalis* as a medicinal-edible homologous substance. Given its chemical constituents, beneficial bioactivities, and inherent safety, *C. officinalis* holds substantial potential for functional food development.

This signifies that *C. officinalis* qualifies as a food with significant health-promoting effects. Therefore, this review systematically summarizes the features of its active components, with a specific focus on its hepatoprotective applications and underlying mechanisms, aiming to provide theoretical foundations for its development of liver-protective functional foods.

2. Summary of the active constituents of *C. officinalis*

The fruit of *C. officinalis* comprises many active components, such as iridoid glycosides, polyphenols, polysaccharides, and other bioactive chemicals (Table 1). The bioactive constituents substantially influence the many functional properties of *C. officinalis.*

Table 1
C. officinalis chemical constituents and functions.

Categories	Compound	Function	References
Iridoid glycosides	Morroniside	Hepatoprotective; antioxidant; anti-inflammatory; hypoglycemic; hypolipidemic; diabetic osteoporosis relief; nephroprotective; neuroprotective	[30,34,35,141,201-205]
	Loganin	Hepatoprotective; antioxidant; anti-inflammatory; hypoglycemic; neuroprotective	[204-207]
	Cornuside	Hepatoprotective; hypoglycemic; neuroprotective	[35,37,201]
	Loganin-(4'-*O*-7")-a-morroniside; 2'-*O*-*p*-coumaroyl-kingiside	Antioxidant; anti-inflammatory	[31,208]
	Sweroside; loganic acid; dehydro-morroniside; isomers of loganin; 7-*O*-ethylmorroniside; isomers of 7-*O*-methylmorroniside; isomers of logmalicid A/B; isomers of cornin; cornusdiglycosides A-J (1-10)	Hypoglycemic (*via* regulating hepatic glucose metabolism)	[33,201]
	7-*O*-Butylmorroniside;7*R*-*O*-methylmorroniside	Neuroprotection	[204-205]
	Cornusides(A-O); williamsoside D; 7*β*-*O*-ethylmorroniside; 7*α*-*O*-ethylmorroniside; 7*α*-*O*-methylmorroniside; 7*β*-*O*-methylmorroniside; 7*α*-morroniside; 7*β*-morroniside; 8-epiloganin	Anticancer	[209]
Anthocyanins	Cyanidin 3-*O*-glucoside	Antioxidant; anti-inflammatory	[24,210]
	Delphinidin 3-*O*-galactoside; cyanidin 3-*O*-galactoside; cyanidin; 3-*O*-robinobioside; pelargonidin 3-*O*-galactoside; pelargonidin 3-*O*-robinobioside; cyanidin; pelargonidin; cyanidin 3-*O*-galactoside; pelargonidin 3-*O*-galactoside; delphinidin 3-*O*-galactoside	Anti-inflammatory; hypolipidemic (*via* hepatic lipid regulation)	[43-44]
Flavonoids	Quercetin 3-*O*-glucoside; kaempferol 3-*O*-glucoside	Antioxidant (hepatic ROS scavenging)	[24,40]
	Quercetin; kaempferol; rutin; dihydroquercetin	Hypoglycemic (*via* hepatic glucose homeostasis)	[46,48,211]
Phenolic acids	Caffeoylquinic acid derivatives; *p*-coumaric acid derivatives	Antioxidant; anti-inflammatory (hepatic inflammation suppression)	[24]
	7-*O*-Galloyl-*D*-sedoheptulose; gallic acid; caffeic acid; gallic acid derivatives; hydroxybenzoic acid	Hypoglycemic (*via* hepatic gluconeogenesis inhibition)	[46,48,211]
Polysaccharides	ECO (Rha, GalA, Gal, Ara); APFC-2 (Rha, GalA, Gal, Ara)	Hypoglycemic; hepatoprotective	[50]
	FCP-3 (Rha, GalA, Gal, Ara); PFC-3 (Glc, Xyl, Gal)	Tumor inhibition (hepatic tumor suppression); immunomodulation; antioxidant	[51]
	FCPC (Man, GalA, Glc, Xyl, Gal, Ara)	hepatic antioxidant defense	[53]
	FCAP1 (Glc, Man, Xyl, Ara, Fuc, Gal); PFC-2 (1,6-*α*-glucans)	Anti-atherosclerosis (*via* hepatic lipid metabolism regulation)	[213-214]
Organic acids	Acetic acid; oxalic acid; malic acid; tartaric acid; citric acid; succinic acid; lactic acid	Hepatoprotective	[13]
Furan derivatives	5-HMF	Hepatoprotective; antioxidant	[63,215]

2.1 Iridoid glycosides

The cornel iridoid glycosides (CIG) constitute the primary components of the fruit. The concentration of cycloartane iridoid glycosides in CM and *C. officinalis* is reported to be 89.09–493.69 and 1 117.01–1 441.22 mg/100 g[29]. Currently, 103 varieties of iridoid glycosides have been isolated and characterized, including loganin, morroniside, sweroside, verbenalin, cornoside, loganic acid, 7*α*-ethylmorroniside, 7*β*-ethylmorroniside, 7*α*-methylmorroniside, 7*β*-methylmorroniside, cornuside A, cornuside B, among others. Cornuside is a unique iridoid glycoside compound in *C. officinalis*, while loganin and morroniside serve as one of the quality control standards for *C. officinalis*. The CIGs have shown significant effects in hepatoprotection[30], antioxidant activity, anti-inflammatory properties[30-31], blood glucose reduction[32-33], lipid-lowering effects[34], anti-osteoporosis[26], kidney protection[35], testicular protection[36], and neuroprotection[37-38].

2.2 Polyphenols

The fruit of *C. officinalis* is abundant in polyphenolic chemicals, including flavonols[29] and phenolic acids[39]. Reported data show that the flavonols content in CM and *C. officinalis* can reach 0.47–10.67 and 8.13–12.57 mg/g, respectively[40]. The total anthocyanins content in CM is approximately 3.05–4.06 mg/g, while the total anthocyanin content in *C. officinalis* is approximately 10.52–17.18 mg/g. Additionally, CM fruits are reported to contain 2.08–2.11 mg/g of ellagic acid. The anthocyanins include pelargonidin, pelargonidin 3-*O*-galactoside, pelargonidin 3-*O*-glucoside, pelargonidin 3-*O*-robinobioside, pelargonidin 3-*O*-rhamnosylgalactoside, pelargonidin 3-*O*-rutinoside, cyanidin, cyanidin 3-*O*-galactoside, cyanidin 3-*O*-glucoside, cyanidin 3-*O*-robinobioside, cyanidin 3-*O*-rutinoside, peonidin 3-*O*-glucoside, delphinidin 3-*O*-glucoside, delphinidin 3-*O*-galactoside, and petunidin 3-*O*-glucoside. Flavonoids include quercetin, quercetin 3-*O*-rutinoside, quercetin 3-*O*-xyloside, quercetin 3-*O*-rhamnoside, quercetin 3-*O*-galactoside, kaempferol 3-*O*-galactoside, catechin, epicatechin, epicatechin 3-*O*-gallate, naringenin, naringenin 3-*O*-methyl ester, and isoquercitrin. *C. officinalis* also contains small amounts of phenolic acids[41], including gallic acid, *p*-coumaric acid, ellagic acid, chlorogenic acid, ferulic acid, and caffeic acid. These substances have demonstrated beneficial effects in hepatoprotection[42], cholesterol reduction[43-44], antioxidant activity[45], improving glucose and lipid metabolism[46], gut microbiota dysbiosis[47], and anticancer properties[48].

2.3 Polysaccharides

Polysaccharides are a key bioactive fraction in *C. officinalis* fruit, accounting for roughly 6.6%–25.2% of the total composition. These polysaccharides primarily consist of acidic and neutral polysaccharides[49]. Monosaccharide composition includes glucose, galactose, arabinose, mannose, xylose, with trace rhamnose and galacturonic acid. These polysaccharides exhibit diverse biological activities, including hepatoprotection[50], hypoglycemic[51], antihyperlipidemic[17], anti-oxidant[52], immune modulation[53], and anti-aging[54], which are attributed to their structural features.

2.4 Other components

Besides the well-defined iridoid glycosides and polysaccharides, *C. officinalis* fruit contains a variety of bioactive compounds. Pentacyclic triterpenic acids, a subclass of glycone-type secondary metabolites, include oleanolic acid, ursolic acid, betulinic acid, and crataegolic acid[55]. These compounds have been demonstrated to exert hepatoprotective effects in numerous studies[56-57], primarily *via* antioxidative stress[58], regulation of lipid metabolism[59-60], and modulation of intestinal flora[61]. Furan derivatives generated during thermal processing, particularly 5-hydroxymethylfurfural (5-HMF), also exhibit hepatoprotective potential. 5-HMF attenuates liver fibrosis by suppressing oxidative stress[62], and alleviate endoplasmic reticulum (ER) stress-induced hepatocyte apoptosis *via* modulation of the PERK-eIF2α signaling pathway[63]. The hepatoprotective effect of *C. officinalis* was also influenced by these active ingredients (Table 2).

Table 2
Hepatoprotective activities and mechanisms of *C. officinalis* representative compounds.

Compound	Category	Activity	Mechanism	References
Morroniside	Iridoid glycoside	Anti-inflammatory; anti-fibrotic	Regulates TGF-β1/Smad3 Activates PPAR-α Enhances LAL	[13]
CIG	Iridoid glycoside complex	Anti-inflammatory, gut-regulating	Inhibits NF-κB/AKT Modulates gut flora	[30]
C. officinalis polysaccharides	Polysaccharide	Immunomodulatory; antioxidant	Enhances SCFA; restores gut barrier; boosts SOD and GSH	[53]
Loganin	Iridoid glycoside	Antioxidant stress; anti-inflammatory	Activates Nrf2/HO-1; inhibits NF-κB; inhibits hepatocyte apoptosis	[96]
Cornuside	Iridoid glycoside	Anti-inflammatory	Inhibits JNK/ERK; blocks MAPK-NF-κB axis; suppresses NKT/T cell activation; promotes G-MDSCs recruitment	[100]
HGK	Flavonoid	Pro-apoptotic (anti-HCC)	Activates Caspase-3 in HCC cells	[165]

3. Hepatoprotective mechanism of *C. officinalis*

The hepatoprotective mechanisms of *C. officinalis* include the reduction of oxidative stress, suppression of excessive inflammatory responses, regulation of lipid metabolism, prevention of excessive hepatocyte apoptosis, inhibition of excessive hepatic stellate cell activation, modulation of gut microbiota homeostasis, and inhibition of hepatocellular carcinoma (HCC) progression (Table 3).

Table 3
C. officinalis chemical constituents and functions.

Bioactive effects	Representative compounds and extracts	Target model	Mechanism	References
Inhibit hepatocyte apoptosis	Loganin	*db*/*db* mouse	↑Bcl-2 protein ↓Bax, Cyt c	[96]
Antioxidant stress	Morroniside	NAFLD mouse	↓TLR4/NF-κB pathway, MDA	[13]
	Iridoid glycosides	INH/RIF induced DILI mice; ethanol induced ALD mice	↑SOD, CAT, GSH ↓MDA, CYP2E1	[30]
	CMO	Ethanol induced ALD mice	↑GSH, SOD, GSH-Px ↓CYP2E1	[78]
	HWCO	SK-Hep1 liver cancer cells	↓XO, ROS	[79]
	Loganin	*db*/*db* mouse	↓Nox-4, p22phox, ROS	[96]
	CWO	CCl_4-induced acute liver injury in mice	↑GSH ↓SOD, MDA	[105]
Anti-inflammatory	COV	NAFLD mouse liver injury model	↑IL-10 ↓TNF-α	[13]
	HWCO	SK-Hep1 liver cancer cells	↓COX-2	[79]
	HPWS	CCl_4-induced acute liver injury in mice	↓NLRP3, Caspase-1 ↓IL-1β, $F4/80^+$	[92]
	Loganin	*db*/*db* mouse	↓NF-κB/AKT pathway	[96]
	Cornuside	ConA Induced AIH mice	↑G-MDSCs ↓JNK, ERK, NKT	[100]
	CWO	CCl_4-induced acute liver injury in mice	↑$F4/80^+$ ↓IL-6, IL-1β, TNF-α, NF-κB COX-2, iNOS ↓MCP-1 transcription	[105]
Regulation of lipid metabolism disorders	COV	NAFLD mouse	↑ATGL ↓PLIN-2	[13]
	Dried powder of *C. officinalis*	MAFLD patient	↓HOMA-IR, HbA1c	[109]
	C. officinalis resin purified extract	NAFLD rabbit	↑ABCA1, ABCG1, LXR-α ↑PPAR-α, PPAR-γ ↓SREBP-1c, C/EBPα, FAS ↓RBP4	[114]
Antitumor	FCP-SeNPs	HepG2 cells H22 tumor mouse	↑TNF-α, IL-12, p70	[53]
	HWCO	HCC cells	↑p53 ↓MAPK ↓PI3K-Akt pathway	[79]
	HGK	BEL-7404 liver cancer cells	↑Caspase-3, PARP1	[165]
Inhibition of hepatic stellate cellactivation	HPWS-CO	CCl_4-Induced acute liver injury in mice	↑SIRT3, p-AMPK ↓IL-1β	[92]
	CWO	CCl_4-Induced acute liver injury in mice	↓TGF-β1/Smad3	[105]

Table 3 (*Continued*)

Bioactive effects	Representative compounds and extracts	Target model	Mechanism	References
Improvement of gut-liver axis homeostasis	CIG	Ethanol induced ALD mice	↑Firmicutes abundance ↑ZO-1, Occludin ↓Bacteroidota abundance ↓LPS	[30]
	COV	NAFLD mouse	↑*Faecalibacterium* ↑*Bifidobacterium* ↑*Lactobacillus* ↑*Ruminococcus* ↓Bacteroidaceae	[34]

Note: ↑ Indicates an upward adjustment; ↓ Indicates a downward adjustment.

3.1 *Attenuation of oxidative stress*

Oxidative stress is a key driver of hepatocyte injury, characterized by excessive reactive oxygen species (ROS) production, which exacerbates cellular damage and induces hepatocyte death. This process contributes to the pathogenesis of multiple liver diseases, including, ischemia-reperfusion injury (IRI)[64], viral hepatitis (VH), alcoholic liver disease (ALD), drug-induced liver injury (DILI), and non-alcoholic fatty liver disease (NAFLD)[65]. *C. officinalis* attenuates oxidative stress through multiple mechanisms: activating the nuclear factor erythroid 2-related factor 2/kelch-like ECH-associated protein 1 (Nrf2/Keap1) signaling pathway (promoting Nrf2 nuclear translocation and heme oxygenase-1 (HO-1) upregulation), inhibiting cytochrome P450 2E1 (CYP2E1) and NADPH oxidase activity, enhancing antioxidant enzyme levels, and reducing peroxide production (Fig. 1).

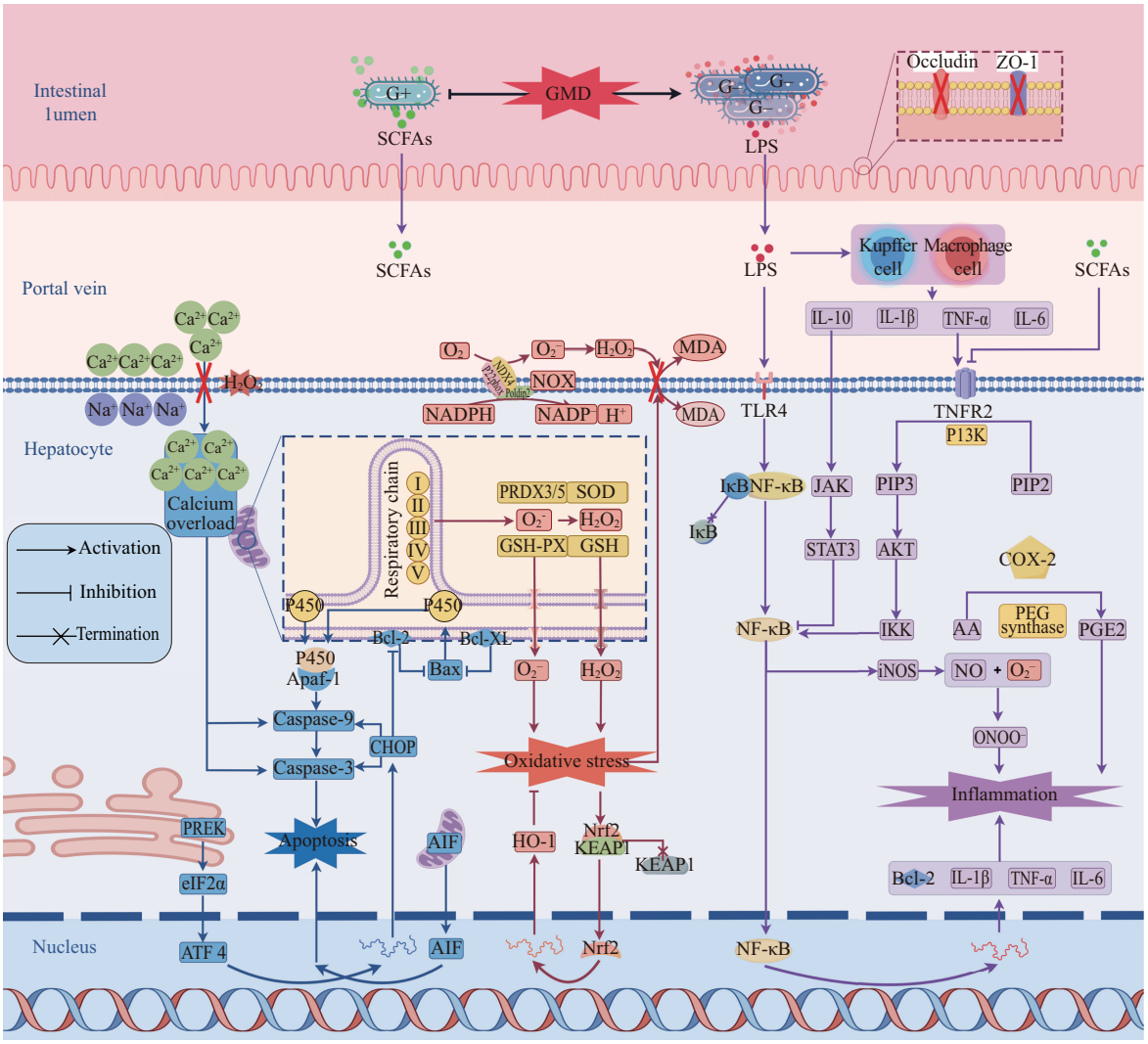

Fig. 1 *C. officinalis* demonstrates hepatoprotective effects through the regulation of hepatocyte apoptosis, oxidative stress, inflammatory response, and intestinal flora.

HO-1 is a critical antioxidant enzyme that degrades heme to biliverdin (converted to bilirubin) and carbon monoxide, enhancing cellular resistance to oxidative stress[66]. The Nrf2/Keap1 signaling pathway is the most important pathway for anti-oxidative stress in the liver[67]. Under oxidative stress, Nrf2 dissociates from Keap1 and translocates into the nucleus, where it forms a heterodimer with small Maf proteins (sMaf). This complex binds to the antioxidant response element (ARE) in the promoter region of target genes, thereby inducing the expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and HO-1[68-69]. By upregulating HO-1 expression, Nrf2 enhances the cellular capacity to detoxify heme-derived oxidative metabolites, thereby alleviating intracellular oxidative stress[70]. The ethanol extract of *C. officinalis* (ECO) alleviated histopathological liver damage, significantly enhanced HO-1 and SOD activities, and mitigated acetaminophen (APAP)-induced oxidative injury in hepatocytes[15]. Supporting this, flavonoids have been shown to ameliorate nicotine-induced liver injury *via* activation of the Nrf2/HO-1 pathway[71]. These findings suggest that the abundant flavonoids in *C. officinalis* are key contributors to its antioxidant activity. Additionally, administration of *C. officinalis* fruit extract (CMFE) at doses of 200, 300, and 500 mg/kg for 14 days significantly reduced malondialdehyde (MDA) levels by approximately 35% in CCl_4-induced rat models. It also restored serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein, and albumin, demonstrating a strong protective effect against chemically induced hepatic injury[72].

CYP2E1, a key cytochrome P450 enzyme predominantly expressed in the liver, is responsible for metabolizing various endogenous and exogenous substrates, including ethanol and environmental toxins[73]. In the process, CYP2E1 can convert these compounds into highly reactive or toxic intermediates, generating substantial amounts of ROS[74-75]. CCl_4, a well-known hepatotoxin, is bioactivated by hepatic CYP2E1 to generate trichloromethyl ($CCl_3\cdot$) and trichloromethyl peroxy ($CCl_3O_2\cdot$) radicals, ultimately leading to hepatocellular injury and necrosis[76]. The iridoids and polyphenols in CMFE exert antioxidant effects by stabilizing hepatocyte membranes and activating the Nrf2/HO-1 pathway. ALD is also associated with CYP2E1 enzyme[77]. CIG reduce hepatic CYP2E1 expression, thereby attenuating oxidative stress caused by ethanol-derived ROS and acetaldehyde[30]. These findings are consistent with studies by Jiang et al.[78], in which *C. officinalis* methanol extract inhibited CYP2E1 activity, elevated hepatic antioxidant enzyme levels glutathione (GSH), SOD, glutathione peroxidase (GSH-Px), and reduced alcohol-induced oxidative stress.

In addition to CIG, studies have shown that *C. officinalis* vinegar (COV) attenuates NF-κB-mediated inducible nitric oxide synthase (iNOS) activation. This leads to reduced production of peroxynitrite ($ONOO^-$), a potent oxidative agent, in hepatic cells, thereby mitigating oxidative stress in NAFLD models[13]. Additionally, hot water extract of *C. officinalis* (HWCO) inhibits xanthine oxidase (XO) activity, thereby reducing ROS formation during purine metabolism[79]. Moreover, loganin downregulates Nox-4 and p22phox expression, key subunits of NADPH oxidase, thereby suppressing constitutive ROS generation and contributing to redox homeostasis[80-81]. This redox regulation by *C. officinalis* contributes to hepatoprotection.

APAP is a common over-the-counter analgesic and antipyretic. Overdose of APAP can lead to the accumulation of *N*-acetyl-*p*-benzoquinone imine (NAPQI), which can induce oxidative stress and liver injury[82]. In the United States, over 50% of pharmaceutical-related acute liver failure (ALF) cases are attributed to APAP overdose[83-84]. Hepatocellular necrosis is pivotal in the context of APAP-induced liver injury (ALI)[85-87]. The ECO significantly reduces plasma levels of AST, ALT, lactate dehydrogenase (LDH), and MDA in APAP-treated mice. It also enhances hepatic SOD and HO-1 activity, improving cellular antioxidant capacity and alleviating APAP-induced hepatotoxicity[15].

3.2 Inhibition of excessive inflammatory responses

Excessive inflammatory responses are a key driver of liver injury and may ultimately lead to liver failure[88]. Inflammation and oxidative stress are closely intertwined, forming a vicious cycle where ROS generation promotes cytokine release, which in turn stimulates further oxidative damage[89-90]. *C. officinalis* alleviates hepatic inflammation by suppressing NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation, reducing interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) secretion, modulating immune cell function, and enhancing granulocytic myeloid-derived suppressor cell (G-MDSC) recruitment (Fig. 1).

Pro-inflammatory cytokines induce macrophage maturation and IL-1β release, a process dependent on NLRP3 inflammasome activation and Caspase-1-mediated cleavage of pro-IL-1β[91]. High-pressure wine-steamed *C. officinalis* (HPWS) inhibits CCl_4-induced NLRP3 activation and Caspase-1 cleavage, reducing IL-1β release and expression of macrophage marker F4/80[92], significantly alleviating hepatic inflammation. Notably, oxidative stress is one of the important upstream signals that activate NLRP3 inflammasome[93]. Oxidative stress serves as an upstream activator of NLRP3, suggesting that HPWS may exert dual antioxidant and anti-inflammatory actions[94]. Future studies can further explore the specific targets and signaling pathways of HPWS to further clarify its therapeutic potential. At the enzymatic level, cyclooxygenase-2 (COX-2) is a central mediator of inflammation, catalyzing arachidonic acid conversion to pro-inflammatory prostaglandins[95]. HWCO inhibits COX-2 activity in liver cancer cells[79]. Centrally, the NF-κB and AKT signaling pathways orchestrate inflammatory responses by regulating gene transcription of pro-inflammatory mediators. Loganin downregulates NF-κB and iNOS expression in diabetic livers thereby suppressing COX-2 and iNOS expression and mitigating insulin resistance-associated liver inflammation[96], while CIG modulates the NF-κB/AKT axis in hepatocytes[97], providing a unified mechanism underlying the anti-inflammatory potential of *C. officinalis* derivatives.

In autoimmune hepatitis (AIH), hyperactivation of natural killer T (NKT) cells drives hepatocyte injury[98]. G-MDSCs mitigate this by suppressing T and NKT cell activity[99]. In Con A-induced AIH mice, *C. officinalis* inhibits c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK) phosphorylation, disrupts the MAPK-NF-κB axis, enhances G-MDSC recruitment, and alleviates immune-mediated liver injury[100]. It is noteworthy that ILI arises from aberrant immune responses that trigger hepatocyte destruction, involving hyperactivation of hepatic immune cells (Kupffer cells, NKT cells, T cells) and subsequent inflammation[101]. This process is central to the progression of ALF[102], cirrhosis[103], and HCC[104].

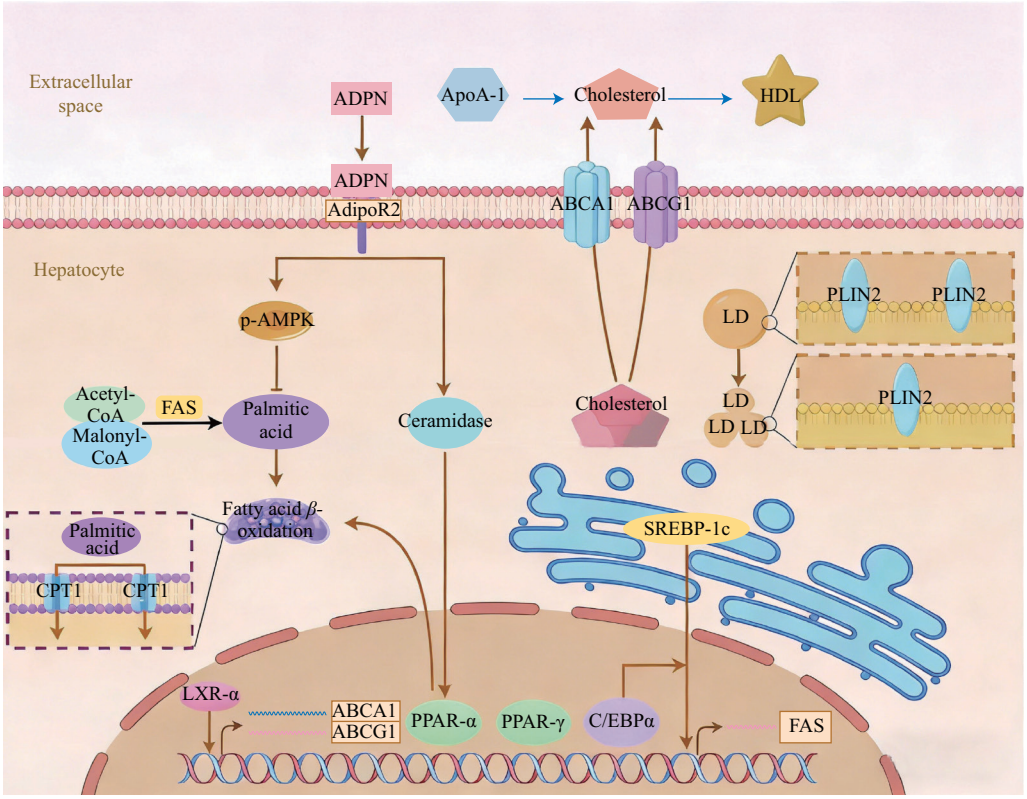

Fig. 2 *C. officinalis* regulates lipid metabolism-related pathways.

C. officinalis oil (CWO) also attenuates macrophage-driven inflammation by reducing F4/80$^+$ macrophage infiltration and hepatic monocyte chemoattractant protein-1 (MCP-1) expression in fibrotic livers, delaying fibrosis progression and dampening innate immune activation[105]. This dual effect on macrophage recruitment and chemokine production alleviates local inflammation and delays liver fibrosis progression, highlighting CWO's role in limiting innate immune cell infiltration.

3.3 Regulation of lipid metabolism disorders

Hepatic steatosis, characterized by excessive lipid accumulation in the liver, is central to both metabolic dysfunction-associated fatty liver disease (MAFLD) and alcoholic fatty liver disease (AFLD). As the redefined concept of NAFLD, MAFLD emphasizes the metabolic disorder component. Globally, the prevalence of MAFLD is as high as 25%−30%[106], which significantly increases the global burden of chronic liver disease[107]. At present, it mainly depends on lifestyle intervention. Meanwhile, AFLD, caused by chronic alcohol consumption, remains a major contributor to liver cirrhosis in Europe and North America[108]. *C. officinalis* and its bioactive constituents exert therapeutic effects on both MAFLD and AFLD by modulating hepatic lipid metabolism at both systemic and molecular levels (Fig. 2).

In a randomized clinical trial, 8-week administration of *C. officinalis* lyophilized powder significantly reduced serum triglycerides, ALT, AST, ALP, and γ-glutamyl transferase levels. Improvements were also observed in hepatic steatosis (27.3% of patients), CRP, fasting glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and HbA1c, indicating restored hepatic glucose-lipid homeostasis[109]. Mechanistically, the aqueous extract of *C. officinalis* (COE) improves mitochondrial bioenergetics and restores tricarboxylic acid (TCA) cycle activity by upregulating glutamate dehydrogenase (GDH)[110]. APFC-2, a pectin polysaccharide derived from *C. officinalis*, activates the LKB1/AMPK pathway, thereby enhancing fatty acid β-oxidation and reducing hepatic lipid accumulation in AFLD models[50]. The LKB1/AMPK pathway is a cellular energy sensor, and its activation can promote fatty acid oxidation, inhibit fatty acid synthesis and lipid production, thereby reducing liver lipid accumulation[111]. AMPK activation promotes acetyl-CoA carboxylase (ACC) phosphorylation and carnitine palmitoyltransferase 1 (CPT-1) expression, leading to reduced triglyceride and cholesterol content in the liver[112].

Decreasing fatty acid production and enhancing fatty acid oxidation are 2 essential strategies for ameliorating lipid metabolism diseases. *C. officinalis* also suppresses lipogenesis by modulating sterol regulatory element-binding protein-1c (SREBP-1c), a key transcription factor for fatty acid synthesis[113]. In hypercholesterolemic rabbits, iridoid- and polyphenol-rich extracts reduced hepatic SREBP-1c and C/EBPα expression by 38% and 42%, respectively, while downregulating fatty acid synthase (FAS) and retinol-binding protein 4 (RBP4)[114]. Simultaneously, these extracts upregulate cholesterol efflux genes ATP-binding cassette transporter A1 (ABCA1) and ABCG1, promoting reverse cholesterol transport and reducing hepatic lipid load[115].

Additionally, *C. officinalis* regulates peroxisome proliferator-activated receptors (PPARs), particularly PPAR-α, which enhances β-oxidation of fatty acids via mitochondrial and peroxisomal gene expression[116]. Adiponectin receptor 2 (AdipoR2) activates this pathway synergistically[117]. *C. officinalis* extract increases hepatic

liver X receptor-alpha (LXR-α), PPAR-α, and PPAR-γ levels, facilitating lipid catabolism and cholesterol efflux[118]. Park et al.[119] further confirmed that morroniside, a major iridoid from *C. officinalis*, suppresses SREBP-1c and upregulates PPAR-α, LXR-α, ABCA1, ABCG1, and AdipoR2, ameliorating hepatic steatosis in NAFLD models. Notably, *C. officinalis*-synthesized gold nanoparticles (GNPs-CM) have been shown to reduce hepatic oxidative stress and inflammation in high-fat diet-fed mice by lowering levels of MDA, TNF-α, IL-1α, and toll-like receptor 4 (TLR4)[120]. Moreover, COV downregulates the lipid droplet protein PLIN-2 and upregulates adipose triglyceride lipase (ATGL), thereby suppressing lipid droplet formation and enhancing triglyceride catabolism[34]. Collectively, these findings underscore the multifaceted role of *C. officinalis* in improving hepatic lipid homeostasis, through pathways involving AMPK, PPARs, SREBP-1c, and reverse cholesterol transport.

3.4 Inhibition of excessive hepatocyte apoptosis

Hepatocyte apoptosis is a critical event in the progression of liver injury and is primarily triggered by mitochondrial dysfunction and ER stress[121]. Targeting apoptotic pathways is considered a promising strategy to limit hepatic damage and promote liver regeneration[122] (Fig. 1).

Apoptosis is tightly regulated through intrinsic and extrinsic pathways, with the mitochondrial (intrinsic) Caspase-dependent route being the most prominent[123]. Under cellular stress—such as oxidative damage, ER stress, or DNA injury—mitochondrial outer membrane permeability (MOMP) increases, facilitating the release of cytochrome c and other pro-apoptotic factors into the cytoplasm. This cascade sequentially activates Caspase-9 and effector Caspase-3, culminating in programmed cell death[124-125]. Several bioactive constituents from *C. officinalis* exhibit anti-apoptotic properties by interfering with this pathway. 5-HMF, a Maillard reaction product found in processed *C. officinalis*[126], downregulates Bax, reduces Caspase-3/9 activities, and suppresses the release of Apaf-1, cytochrome c, and apoptosis-inducing factor (AIF) in TNF-α/*D*-GalN-induced hepatocytes[63]. Similarly, loganin inhibits mitochondrial apoptotic signaling in *db/db* mice by decreasing Bax and cytochrome c expression while enhancing anti-apoptotic Bcl-2 levels[96]. This results in reduced Caspase-9 and Caspase-3 activation, effectively mitigating hyperglycemia-induced hepatocyte apoptosis. However, the precise role of the complex regulatory network of apoptosis, especially Bcl-2 family proteins and ERS-related signaling pathways, is unclear and needs to be further elucidated in the future.

3.5 Inhibition of excessive hepatic stellate cell activation

Liver fibrosis represents a reversible wound-healing response to chronic liver injury, primarily driven by activation of hepatic stellate cells (HSCs) and dysregulated extracellular matrix (ECM) deposition *via* the transforming growth factor-beta 1 (TGF-β1)/Smad3 signaling pathway[63]. Unmanaged fibrosis progresses to cirrhosis and HCC, involving hepatocyte necrosis, architectural damage, and liver dysfunction[128]. *C. officinalis* exerts anti-fibrosis effects by regulating mitochondrial energy homeostasis (SIRT3-AMPK axis), inhibiting ECM turnover to promote apoptosis of HSCs, regulating lysosomal acid lipase (LAL)-mediated lipid metabolism, and inhibiting TGF-β1/Smad3 signaling pathway (Fig. 3).

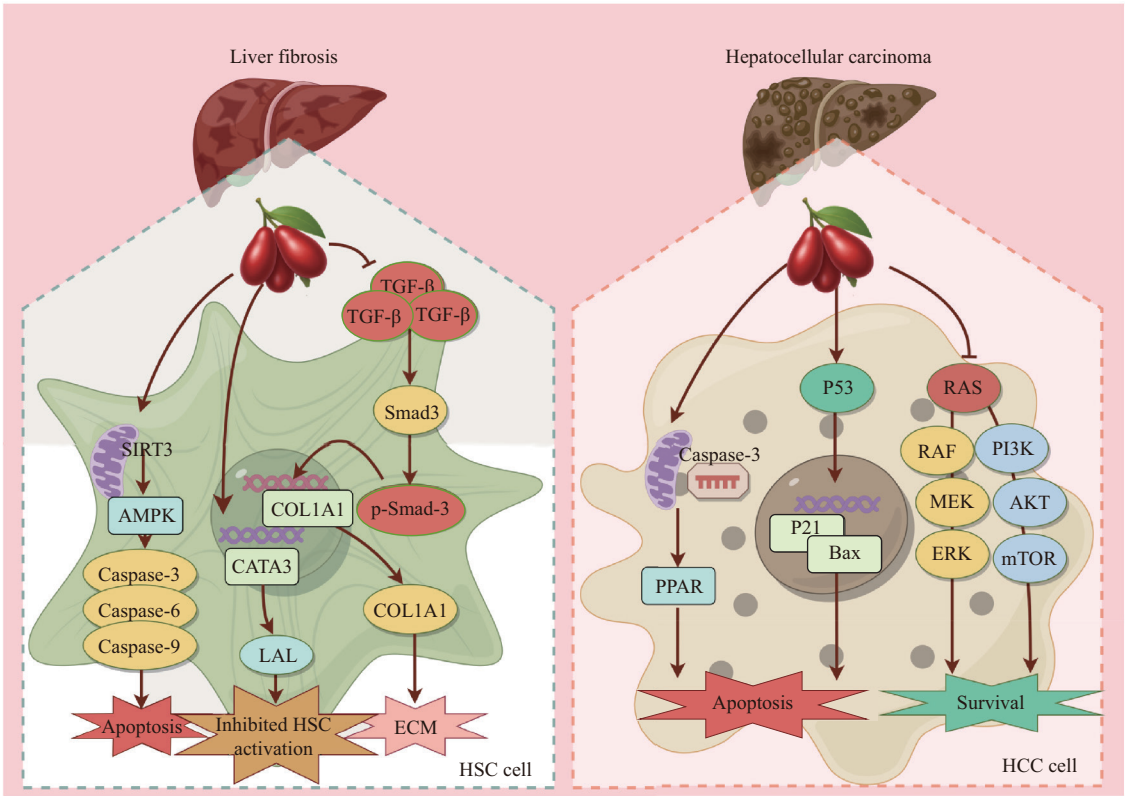

Fig. 3 *C. officinalis* modulates signaling pathways in HSC and HCC.

Targeting HSC activation is a pivotal antifibrotic strategy[129]. Mitochondria play a central role in maintaining the structural and functional integrity of hepatocytes and HSCs[130], and their dysfunction almost runs through the pathological process of most liver diseases[131]. The AMPK signaling pathway, a master regulator of cellular energy homeostasis, exerts antifibrotic effects by mitigating inflammation, suppressing HSC activation, and limiting ECM overproduction[132]. Sirtuin 3 (SIRT3), a mitochondrial NAD^+-dependent deacetylase, activates AMPK and modulates hepatocyte metabolism and apoptosis[133-134]. HPWS enhances SIRT3-AMPK signaling, leading to Caspase-3/6/9 activation in HSC-T6 cells and promoting HSC apoptosis, thereby attenuating liver fibrosis[92]. These effects may arise from processing-induced iridoid degradation, which improves the bioavailability and efficacy of active compounds[135-136].

Aberrant hepatic lipid metabolism is also closely linked to fibrosis progression[137-138]. LAL plays a key role in intracellular lipid turnover by hydrolyzing triglycerides and cholesterol esters within lysosomes[139]. LAL deficiency exacerbates hepatic lipid accumulation and fibrosis[140]. Morroniside enhances LAL expression and activity by disrupting the GATA3-Lipa inhibitory axis: it binds the GATA3 hydrophobic domain and downregulates its expression, thereby lifting transcriptional repression of Lipa and increasing LAL-mediated lipid catabolism[141]. These mechanisms collectively reduce ECM accumulation and HSC activation.

Moreover, *C. officinalis* inhibits the profibrotic TGF-β1/Smad3 pathway. TGF-β1/Smad3 signaling pathway is the key driver of HSC activation[143-144]. Upon ligand binding, TGF-β1 induces Smad3 phosphorylation at Ser423/425, promoting *α*-smooth muscle actin (*α*-SMA) and collagen type I alpha 1 chain (COL1A1) expression[144]. In TGF-β1-induced HSC-T6 cells, morroniside inhibits *α*-SMA expression in a dose-dependent manner[141]. Similarly, CWO inhibits TGF-β1/Smad3 signaling by suppressing Smad3 phosphorylation at Ser423/425, reducing HSC activation and collagen I deposition[105]. CWO also lowers serum levels of fibrosis biomarkers such as hyaluronic acid (HA), procollagen I (PCI), type IV collagen (IV-C), and laminin (LN). Interestingly, sarracenin (SA)-a deglycosylated derivative of morroniside-exhibits 2.1-fold higher Smad3 inhibition than its glycosylated counterpart, attributed to its enhanced lipophilicity and improved cellular uptake. This supports the enhanced antifibrotic efficacy of processed *C. officinalis* in traditional Chinese medicine formulations. Mechanistically, morroniside's deglycosylation during processing increases SA's lipophilicity. These effects collectively strengthen hepatocyte protection and fibrosis inhibition.

Given the central role of HSCs in fibrogenesis, emerging strategies now focus on targeting these cells using nanotechnology. Dual-drug nano-delivery systems co-loaded with curcumin and dihydromyricetin, as well as engineered milk-derived exosomes encapsulating phillygenin, have demonstrated targeted antifibrotic effects by inhibiting HSC activation[146-147]. These advances, in conjunction with natural products like *C. officinalis*, represent promising avenues for antifibrotic therapy.

3.6 Modulation of gut microbiota homeostasis

The gut-liver axis is a critical pathway in liver disease, where gut microbiota dysbiosis exacerbates hepatic injury *via* metabolite-mediated crosstalk[147]. Gut microbiota dysbiosis disrupts homeostasis, alters hepatic immune status, and drives the development of various liver diseases[149-150]. This imbalance is manifested in the decrease of beneficial bacteria and the increase of harmful bacteria[150] (Fig. 1).

C. officinalis and its derivatives have been shown to restore gut microbial composition and diversity. COV markedly enhances intestinal biodiversity in high-fat diet-fed mice, increasing beneficial genera such as *Faecalibaculum*, *Bifidobacterium*, and *Lactobacillus*, while correcting imbalances in Bacteroides and Lachnospiraceae abundance[30]. Similarly, CIG reverse alcohol-induced gut dysbiosis by restoring the Firmicutes/Bacteroidota ratio and reducing Verrucomicrobia levels. At the genus level, CIG upregulates *Lactobacillus* while suppressing overrepresented Muribaculaceae and Desulfovibrionaceae[30]. CNBP also modulates gut microbial ecology by restoring depleted genera such as *Lactobacillus*, *Romboutsia*, *Turicibacter*, and *Anthrobacter*, while suppressing pathogenic taxa including *Escherichia*, *Enterococcus*, and *Aspergillus* elevated in CCl_4-induced liver injury models[151].

Dysbiosis-induced shifts in microbial metabolites further contribute to liver injury[152]. Under pathological conditions, the increase of intestinal Gram-negative bacteria will increase the production of lipopolysaccharide (LPS) and intestinal permeability, which will lead to the infiltration of LPS into the portal vein[153], stimulate the secretion of pro-inflammatory cytokines by immune cells, and aggravate liver injury[154]. Conversely, short-chain fatty acids (SCFAs)—notably acetate, propionate, and butyrate—support intestinal barrier function and liver health by promoting regulatory T-cell differentiation, activating G protein-coupled receptor 43/41 (GPR43/41) receptors, and suppressing hepatic NLRP3 inflammasome activation[30,156]. CNBP also elevates intestinal SCFA levels and restores key bacterial populations, further supporting the gut-liver axis and contributing to hepatoprotection[151].

These findings underscore the regulatory role of *C. officinalis* in gut microbial composition and function, providing a mechanistic basis for its protective effects on the liver *via* modulation of the gut-liver axis.

3.7 Inhibition of HCC progression

HCC is among the most prevalent and rapidly progressing malignancies worldwide[158-159]. Its development is associated with multiple risk factors, including chronic viral infections, metabolic disorders, obesity, alcohol intake, autoimmune diseases, and chronic inflammationIn addition to viral infections such as hepatitis B virus (HBV)[160-161]. *C. officinalis* directly inhibit HCC cell proliferation by modulating the Caspase-3-mediated apoptotic pathway (PARP cleavage) and targeting the oncogene Ras and tumor suppressor gene *p53* (Fig. 3).

Signaling pathways regulating tumor cell proliferation and apoptosis are primary targets for antitumor drugs that induce tumor cell apoptosis[161]. Caspase-3, as a cysteine aspartic acid-specific protease, plays a key role in apoptosis[162]. Several natural extracts induce HCC cell apoptosis by activating the mitochondrial pathway to trigger Caspase-3 cleavage[164-165]. Hydroxygenkwanin (HGK), a flavonoid isolated from *C. officinalis*, has been shown to dose-dependently increase Caspase-3 activity and promote apoptosis in BEL-7404 liver cancer cells[165].

Additionally, *C. officinalis* targets key molecular drivers of tumorigenesis. The Ras gene family, frequently mutated in HCC,

regulates cell proliferation and survival through the Raf/MEK/ERK and PI3K/AKT/mTOR signaling cascades[167-169]. Conversely, p53 is a powerful tumor suppressor that mediates a wide range of stress responses from survival to cell death[169], which also involved in the process of liver tissue damage and repair[170]. Ras and p53 exhibit regulatory crosstalk critical for carcinogenesis. HWCO inhibit HCC cell proliferation by downregulating Ras expression and upregulating p53, thereby disrupting the oncogene-tumor suppressor axis[79]. Selenium nanoparticles (SeNPs) constitute a novel biosynthetic product with low toxicity and high biocompatibility. A substantial amount of research has recognized its potential to enhance anti-tumor activity as a prospective cancer therapeutic agent[171]. Polysaccharide-selenium nanoparticles (FCP-SeNPs) obtained from *C. officinalis* were found to stimulate RAW264.7 cells, resulting in the release of NO, TNF-α, and IL-12p70, which indirectly triggered death in HepG2 cells[53]. *In vivo*, FCP-SeNPs elevate serum TNF-α and IL-12p70 levels and improve the $CD4^+/CD8^+$ T-cell ratio in H22 tumor-bearing mice, resulting in significant tumor growth suppression.

The combined targeting of apoptotic and immune mechanisms highlights the promise of *C. officinalis* as a multi-functional anticancer agent. Its low toxicity and broad-spectrum bioactivity render it a compelling candidate for complementary HCC therapy. Future investigations should focus on clarifying molecular targets, validating *in vivo* efficacy, and exploring potential for reversing sorafenib resistance *via* modulation of ABC transporters.

4. Application prospect of *C. officinalis* as hepatoprotective agent

With the rising prevalence of chronic liver diseases such as NAFLD and immune-mediated hepatic injury, there is increasing market demand for functional foods with hepatoprotective properties[162]. Against this backdrop, *C. officinalis*, a traditional medicinal and edible plant, has garnered growing attention as a promising candidate. In 2023, it was officially included in the *Chinese National List of Medicinal and Edible Substances*[173], providing a regulatory foundation for its functional food development.

Phytochemical analyses reveal that *C. officinalis* is rich in iridoid glycosides, triterpenoids, and polyphenols, these bioactive compounds that exert multifaceted regulatory effects on liver function through synergistic mechanisms. Toxicological studies demonstrate a favorable safety profile, with no significant adverse effects observed at standard dietary intake levels. The recommended daily intake for adults ranges from 6 to 12 g, and there was no obvious adverse reaction in mice at the dose of 500 mg/kg[15], supporting the rationale for long-term consumption and dosage design in functional food development.

Recent advances in *C. officinalis* bioactivity research have highlighted its potential in developing hepatoprotective functional foods. Studies show that fermentation, polyphenol bioavailability enhancement, and bioactive component enrichment can significantly enhance its antioxidant and metabolic regulatory properties. For instance, fermentation with *Bacillus subtilis* an *Bifidobacterium bifidum* markedly increases gallic acid content[174], while fermentation with Zymaflore FX10 could increase the content of protocatechuic acid, total iridoid glycosides and other active components[175]. These fermented products have been developed into value-added beverages: derived alcoholic beverages and compound fruit wines exhibit enriched polyphenol profiles and elevated antioxidant capacities[177-178]. Additionally, *C. officinalis* based honey wine[178], vinegar[24], and even dark chocolate[179] formulations exhibit beneficial modulation of taste perception and bioactivity.

Despite its significant potential, challenges remain in improving the stability and bio accessibility of *C. officinalis*' key phytochemicals for functional food applications. UPLC-MS/MS studies confirm that loganin from *C. officinalis* exhibits an oral bioavailability of only 9.13% in rats[180], and the glycosidic structure of iridoid glycosides renders them susceptible to intestinal enzymatic digestion, resulting in low bioavailability (< 15%)[181]. These pharmacokinetic limitations necessitate advanced delivery strategies. Promising solutions include nanoencapsulation, liposomal carriers, stimuli-responsive hydrogels, and emulsification systems. For example, chitosan oligosaccharide nano-formulations enhance loganin oral bioavailability by 2.3-fold[182], and silymarin-phospholipid complexes improve absorption by 4.5-fold[183]. Other technologies, such as chitosan-glycolipid nanogels (encapsulation efficiency > 85%)[184], pH-responsive liposomes[185], and oil-in-water emulsions, have increased curcumin bioavailability by up to 200%[186].

These delivery systems offer viable pathways for product development. *C. officinalis* polyphenols and iridoids may be incorporated into instant-dissolving granules, effervescent powders, or functional beverages for adjuvant support in alcohol-induced liver injury. Sports supplements targeting fatty liver could be co-formulated with phytosterols and encapsulated polysaccharides to enhance efficacy and shelf stability[187].

Notably, fermentation technology remains critical for *C. officinalis* processing. Current fermentation of *C. officinalis* predominantly relies on a limited range of microbial strains, such as *Lactobacillus* spp. and yeasts, with insufficient microbial diversity constraining the variety of functional metabolites produced. Recent studies show that fermentation with *B. subtilis* and *B. bifidum* significantly increases iridoid glycosides and organic acids[174], attributed to their specific enzymatic hydrolysis capacities. Supporting evidence from pollen fermentation studies confirms that multi-strain co-fermentation can convert bioactive compounds, improving antioxidant and anti-inflammatory activities[188]. Future research may explore non-conventional strains to enzymatically modify iridoid structures *via* their extracellular enzyme systems. Fermented *C. officinalis* products can be tailored to enhance specific health benefits by targeting bioactive enrichment (e.g., increased iridoid glycosides, organic acids, and SCFAs), with potential formats including probiotic beverages, fermented fruit pastes, functional gummies, and nutraceutical powders. Additionally, integrating *C. officinalis* fermentation into prebiotic-probiotic synbiotic systems could synergistically improve gut health and reduce systemic inflammation. With appropriate strain selection and process optimization, these novel fermented products could serve preventive and therapeutic roles, addressing consumer demands for natural, multifunctional health-promoting foods.

Finally, current research trends are actively exploring the combination of digital health platforms, artificial intelligence driven recommendation engines, and personalized nutrition technologies with traditional medicinal plants to achieve precise liver-protecting interventions[189]. The core advantage of this integration is to use AI to optimize the formulation and intake plan of bioactive components, and can be adjusted in real time according to individual metabolic

characteristics and liver function indicators. The combination of *C. officinalis* and AI-driven platforms is expected to lay the foundation for the next generation of personalized medical solutions, especially in the field of precise liver-protecting interventions[190]. By integrating individual intestinal flora characteristics, serum biomarkers and lifestyle parameters, the AI-optimized formulation of bioactive components of *C. officinalis* can be administered through an intelligent delivery system. Such personalized interventions are particularly important for the management of NAFLD and metabolic syndrome. Finally, the collaborative integration of traditional medicinal and edible homologous substances and AI platforms provides a scalable data-driven basis for the next generation of personalized medical solutions.

5. Discussion and conclusion

The liver, as a central metabolic hub, is increasingly burdened by modern dietary and lifestyle factors, intensifying the risk and progression of liver diseases. This has catalyzed the global pursuit of safe, effective hepatoprotective agents. Among them, *C. officinalis* has emerged as a compelling candidate, owing to its traditional medicinal use and growing experimental evidence demonstrating hepatoprotective and nephroprotective activities.

This review comprehensively outlines the multifactorial hepatoprotective effects of *C. officinalis*, highlighting its promise for functional food development. The mechanisms encompass: alleviating oxidative stress *via* Nrf2/HO-1 activation and antioxidant enzyme enhancement; modulating excessive inflammation by inhibiting NLRP3 inflammasome and NF-κB signaling; supporting lipid metabolism balance through regulating SREBP-1c/PPAR-α/LXR-α to mitigate dietary-induced steatosis; protecting hepatocytes from excessive apoptosis *via* balancing Bax/Bcl-2 and Caspase activity; mitigating fibrotic tendencies by suppressing HSC activation (SIRT3-AMPK, TGF-β1/Smad3); strengthening gut-liver crosstalk through enriching beneficial microbiota, enhancing intestinal barrier function, and promoting SCFAs; and fostering cellular resilience *via* bioactive components like iridoids and polyphenols. Collectively, these multi-target effects provide a strong rationale for its application in NAFLD, liver fibrosis, and related chronic liver disorders.

Despite extensive evidence supporting the hepatoprotective potential of *C. officinalis*, key challenges remain. First, the bioavailability and precise mechanisms of its major bioactive components, especially iridoid glycosides, are insufficiently elucidated. Notably, loganin exhibits poor oral bioavailability (9.13%)[191]. The direct relationship between the active form of intestinal flora-mediated glycoside hydrolysis and *in vivo* metabolic transformation and hepatoprotective effects has not been clarified. *In vivo*, these compounds undergo hydrolysis by *β*-glucosidase enzymes derived from the gut microbiota, liberating glucosyl groups to form moderately polar aglycones. These aglycones subsequently experience multiple metabolic transformations including taurine conjugation, glucuronidation, deglycosylation, dehydration, hydroxylation or dehydroxylation, methylation or demethylation, and acetylation, ultimately yielding diverse metabolic derivatives[192-193]. These metabolites, characterized by lower polarity and higher membrane permeability, may exert superior bioactivity. For instance, loganin aglycone and dehydrated morroniside aglycone demonstrate notable anti-inflammatory and anti-cancer properties[195-196]. However, their direct roles in hepatoprotection remain to be conclusively established. Additionally, traditional processing alters iridoid structures, analogous to catalpol degradation in *Rehmannia glutinosa*, potentially enhancing activity[196]. Yet, systematic evaluations on how processing modulates structure-activity relationships remain scarce. In addition, the relationship between polysaccharides and polyphenols on liver protection is not clear. Studies have shown that polysaccharides from various sources, such as grape pomace polysaccharides[197], peach gum polysaccharides[198], and *Pueraria lobata* polysaccharides[199], have shown significant hepatoprotective effects. *C. officinalis* polysaccharide also has a certain hepatoprotective effect. However, both polysaccharides and polyphenols are active ingredients widely present in natural products[200]. They often coexist in plants. Polyphenols are often co-extracted when extracting polysaccharides, and they themselves have significant hepatoprotective activity. Before the evaluation of biological activity, it is necessary to ensure the high purification of *C. officinalis* polysaccharide samples, especially to remove polyphenols. This can be achieved by combining a variety of efficient purification techniques. It can eliminate the effect to the greatest extent and clarify the independent contribution and mechanism of action of polysaccharides in liver protection more clearly. Subsequently, the relationship between the structural characteristics of *C. officinalis* polysaccharides and their hepatoprotective activity was studied in depth to reveal the role of specific structural groups in hepatoprotective activity. In the future, this series of studies provide a solid scientific basis for the development of new hepatoprotective drugs and functional foods based on *C. officinalis* polysaccharides.

Secondly, the existing research has certain limitations. Most mechanistic insights derive from CCl_4-induced liver injury or high-fat diet-induced steatosis in rodents, which poorly recapitulate the multifactorial pathology of human liver diseases often complicated by metabolic syndrome. Furthermore, inconsistencies between *in vitro* and *in vivo* dosage-response relationships raise concerns about the translational reliability of these models. Clinical validation remains scarce; to date, only 1 randomized trial reported that freeze-dried *C. officinalis* improved hepatic steatosis in 27.3% of patients, but lacked detailed methodology, sample size disclosure, and follow-up. Long-term safety data are also insufficient; although oral administration of 500 mg/kg in mice showed no toxicity, the human tolerance profile, particularly over ≥ 6 months and with respect to renal function, remains unassessed.

Third, mechanistic investigations are fragmented, often confined to isolated pathways such as Nrf2 or NF-κB, while the progression of liver disease involves cross-regulation of oxidative stress, inflammation, and gut microbiota. A systems-level "multi-target network modulation" model has yet to be constructed. Additionally, processing-induced changes in chemical structure and activity are underexplored. On the technological front, current advances in fermentation and nanoencapsulation remain at laboratory scale, hindered by high costs and limited fermentation strain diversity—non-conventional microbes such as *Aspergillus* species have not yet been harnessed for their enzymatic potential in metabolite transformation.

This review systematically synthesizes the chemical constituents, hepatoprotective mechanisms, and application prospects of *C. officinalis*, laying a robust foundation for advancing research and

functional food development. Future endeavors should prioritize: 1) Elucidating the metabolism and structure-activity relationships of iridoids using integrated metabolomics and microbiome sequencing to map biotransformation pathways and identify key bioactive aglycones; 2) Strengthening clinical translation and safety assessment through multicenter randomized controlled trials in patients with NAFLD, incorporating dose gradients, while simultaneously monitoring serum markers (ALT, AST, HA, IV-C) and gut microbiota composition; long-term toxicological studies in animal models should evaluate organ-specific outcomes to support recommended human intake levels; 3) Developing integrated fermentation-delivery systems by combining probiotic-mediated biotransformation of iridoid glycosides with pH-responsive liposomal carriers for targeted hepatic delivery and improved bioavailability. Given its multi-mechanistic efficacy, low toxicity, and compatibility with advanced technologies, *C. officinalis* holds great promise as a next-generation hepatoprotective agent in both nutraceutical and pharmaceutical domains.

Declaration of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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