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REVIEW

Role of Curcumin in Chronic Liver Diseases: A Comprehensive Review

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Abstract: Chronic liver disease is a major global health concern, posing significant challenges due to its asymptomatic progression and the limitations of conventional treatments. Effective therapeutic strategies remain a pressing need. Curcumin, a natural polyphenolic compound derived from turmeric rhizomes, has demonstrated diverse pharmacological properties. Beyond its well-known antioxidant activity, curcumin exhibits anti-inflammatory, antiviral, and anti-fibrotic effects, along with the ability to regulate cellular autophagy and apoptosis. Recent studies suggest its potential to inhibit the progression of chronic liver disease through multiple molecular pathways. This review summarizes the latest research on curcumin's therapeutic effects in chronic liver disease, focusing on its mechanisms of action and clinical relevance. By integrating findings from experimental and clinical studies, we aim to provide novel insights into curcumin as a promising therapeutic candidate for liver disease management.

Keywords: curcumin, chronic liver diseases, molecular mechanism, research progress

Introduction

Chronic liver disease (CLD) is a major global health challenge and one of the leading causes of mortality worldwide. According to WHO data, liver disease is now the second leading cause of death after ischemic heart disease.[1] CLD is a broad term encompassing various liver disorders, including alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), viral hepatitis, drug-induced liver injury (DILI), hepatic fibrosis (HF), and hepatocellular carcinoma (HCC).[2] The pathogenesis of CLD typically involves hepatic metabolic dysregulation, chronic inflammation, and cellular damage, leading to abnormal extracellular matrix (ECM) deposition and liver fibrosis. As the disease progresses to cirrhosis, dysplastic nodules form and gradually develop into precancerous lesions. With the accumulation of cytogenetic and epigenetic abnormalities, HCC represents the ultimate stage of CLD.[3–5] The clinical diagnosis and treatment of chronic liver diseases face significant challenges, including limited therapeutic efficacy, adverse effects, and the insidious progression of the disease.[6] In response, natural products have gained increasing attention for liver disease treatment due to their multi-targeted mechanisms and superior safety profiles compared to synthetic drugs.

Curcumin, a bioactive compound derived from the rhizome of turmeric, is often referred to as a "miracle nutraceutical". In addition to turmeric (*Curcuma longa L.)* from the Zingiberaceae family, curcumin is also found in *Curcuma aromatica Salisb., C. zedoaria (Berg.) Rosc*., and *Acorus calamus L*.[7] Structurally, curcumin is a natural phenolic antioxidant with a diketone moiety, featuring both unsaturated aliphatic and aromatic groups in its main chain and a diarylheptanoid backbone. It has a molecular formula of $C_{21}H_{20}O_6$, a molecular weight of 368.37 g/mol and a melting point of 176–178°C. Curcumin appears as an orange-yellow crystalline powder, exhibiting poor solubility in water and ether. It is commonly extracted using alcohol-based methods, as well as acid-base and enzymatic extraction techniques.[8,9] Curcumin is a pleiotropic modulator of multiple signaling pathways, capable of targeting cell surface molecules and exerting protective effects across various organs and systems, including the digestive, nervous, and cardiovascular

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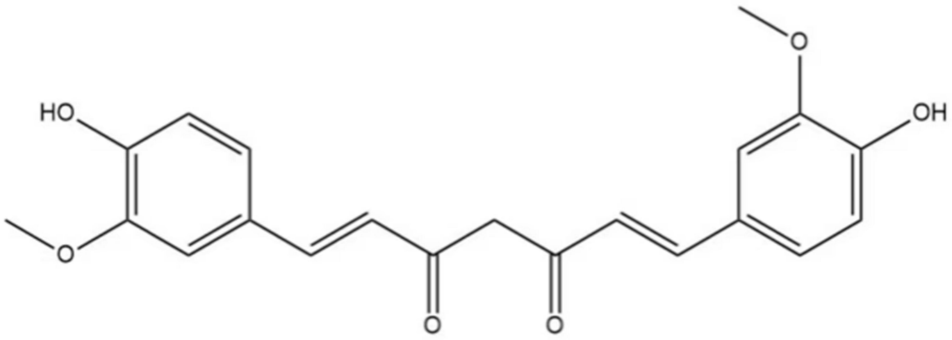

Figure 1 Curcumin chemical structure.

systems.[10] With advancing research, curcumin has demonstrated significant therapeutic potential in CLD, exhibiting antioxidant, anti-inflammatory, antiviral, and anti-fibrotic properties, as well as bidirectional regulation of cellular autophagy and apoptosis. These pharmacological effects contribute to the inhibition of CLD progression.

Given its multifaceted biological activities, elucidating the mechanisms of curcumin in CLD holds great clinical significance. This review provides a comprehensive summary of recent research advances on curcumin's therapeutic applications in CLD, aiming to offer novel insights and potential strategies for its clinical management Figure 1.

The Role of Curcumin in Chronic Liver Diseases

Alcoholic Liver Disease

Alcoholic liver disease (ALD) is a metabolic disorder caused by chronic excessive alcohol consumption.[11] It initially manifests as alcoholic fatty liver and may progress to alcoholic hepatitis, liver fibrosis, cirrhosis, and, in severe cases, liver failure.[12] Ethanol metabolism in the human body primarily relies on oxidative pathways, including alcohol dehydrogenases (ADHs) and the microsomal ethanol oxidizing system (MEOS). Upon ingestion, ethanol is oxidized to toxic acetaldehyde by ADHs, which is subsequently converted to less toxic acetic acid by acetaldehyde dehydrogenases (ALDH). MEOS-mediated ethanol metabolism, predominantly involving cytochrome P450 enzymes (especially CYP2E1), is significantly upregulated in response to high ethanol intake. However, CYP2E1-mediated ethanol metabolism generates excessive ROS, depleting antioxidants such as GSH, triggering lipid peroxidation, and ultimately leading to hepatocellular injury.[13,14] Animal studies have demonstrated that curcumin (0.02% and 0.05% wt/wt for six weeks) can reverse alcohol-induced suppression of ADH and ALDH activity, downregulate CYP2E1 expression, and enhance the activities of SOD, CAT, and GSH-Px, thereby promoting ethanol catabolism and mitigating alcohol-induced liver injury.[15] Similarly, Rong et al found that curcumin (75 mg/kg/day for six weeks) reduced ROS accumulation and counteracted lipid peroxidation in ALD.[16] Excessive ethanol intake also induces hepatic steatosis through multiple pathways.[17] Guo et al reported that curcumin (60 mg/kg for four weeks) ameliorated alcohol-induced hepatic steatosis by modulating fatty acid metabolism, particularly inhibiting lipid biosynthesis and carbohydrate metabolic pathways such as the pentose phosphate and pyruvate metabolism pathways.[18] In a chronic alcohol consumption and high-fat diet-induced liver injury model, curcumin upregulated AMPK expression, inhibited PAP and FAS activities, and reduced plasma levels of leptin, FFA, TG, and the TC/HDL-C ratio, thereby regulating lipid metabolism.[15] Moreover, curcumin (100, 200, and 400 mg/kg for four weeks) inhibited ethanol-induced necroptosis and apoptosis of hepatocytes by activating Nrf2, downregulating p53 expression, and inhibiting JNK and MLKL phosphorylation in a dose-dependent manner. Additionally, it reduced necroptosis markers, including HMGB1, RIP1, and RIP3, further highlighting its hepatoprotective effects.[19]

Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disorder characterized by excessive fat accumulation in hepatocytes, independent of alcohol consumption or other well-defined causes of liver damage. It is closely associated

with metabolic syndromes such as obesity, type 2 diabetes, hyperlipidemia, and hypertension.[20] NAFLD is a progressive disease, with hepatic steatosis (affecting >5% of hepatocytes) as its initial stage, followed by non-alcoholic steatohepatitis (NASH), which is characterized by hepatocellular injury (marked by hepatocyte ballooning), inflammation, and varying degrees of fibrosis.[21] Emerging evidence suggests that curcumin, due to its lipid-lowering, insulin-sensitizing, antioxidant, and anti-inflammatory properties, may reduce the incidence and severity of NAFLD.[22] In a randomized placebo-controlled trial, curcumin supplementation (70 mg/day for 8 weeks) significantly decreased hepatic fat content, body mass index (BMI), serum TC, LDL, TG, AST, ALT, glucose, and glycated hemoglobin (HbA1c) levels.[23] One of the mechanisms underlying NAFLD progression involves the activation of 11beta-hydroxysteroid dehydrogenase 1 (11beta-HSD1), which locally regulates glucocorticoid (GC) activity in the liver and adipose tissue, exacerbating lipid deposition. In a high-fat diet (HFD)-induced metabolic syndrome rat model, curcumin (200 mg/kg for two months) selectively inhibited 11beta-HSD1, modulating GC levels and improving glycolipid metabolism.[24] Another key driver of lipid accumulation is de novo lipogenesis (DNL), where SLC13A5, mitochondrial citrate carrier (SLC25A1), and ATP-citrate lyase (ACLY), determine acetyl-CoA availability—a central substrate for DNL. In OPA-induced and high-fructose, high-fat diet (HFHFD)-fed NAFLD models, curcumin (50 or 150 mg/kg for 6 weeks) indirectly downregulated SLC13A5 and ACLY expression by activating the AMPK-raptor-mTOR signaling pathway, thereby modulating hepatic lipid synthesis.[25] Additionally, AMPK activation by curcumin upregulated PPAR-alpha expression while inhibiting SREBP-1, key regulators of lipid metabolism. SREBP-1c promotes fatty acid and TG synthesis, whereas PPAR-alpha facilitates lipid homeostasis by reducing circulating TG and increasing HDL cholesterol levels.[26] Notably, PPAR-alpha and SREBP-1 expression were also modulated by the Notch signaling pathway, with curcumin (100 or 200 mg/kg/day for 8 weeks) inhibiting Notch-1 to regulate PPAR-alpha/gamma and SREBP-1 levels.[27] Furthermore, curcumin administration decreased serum fetuin-A expression, a protein linked to adiposity and metabolic dysregulation.[28]

In the advanced stage of NAFLD progression, curcumin continues to demonstrate significant therapeutic efficacy. Studies have shown that curcumin mitigates fat accumulation, modulates inflammation, enhances antioxidant defense, and prevents fibrosis, primarily through the inhibition of the Nrf2/ARE and NF-κB signaling pathways, thereby exerting protective effects against NASH.[29] In a NAFLD rat model, curcumin administration (50 mg/kg for 6 weeks) reduced serum levels of inflammatory cytokines, TG, TC, and FFA by inhibiting the Nrf2-Keap1 signaling pathway. Furthermore, curcumin decreased MDA presence, increased GSH and HO-1 levels, and regulated oxidative stress by enhancing SOD activity.[30] In a methionine- and choline-deficient (MCD) diet-induced NASH mouse model, curcumin (100 mg/kg for 8 weeks) effectively suppressed M1 macrophage activation, leading to reduced expression of pro-inflammatory cytokines IL-1beta and TNF-alpha, thereby attenuating hepatic inflammation and liver injury in NASH.[31]

Viral Hepatitis

Viral hepatitis is a significant global health burden, characterized by chronic inflammation that predisposes patients to hepatic fibrosis and HCC. Curcumin has demonstrated potential antiviral effects against both hepatitis B virus (HBV) and hepatitis C virus (HCV). Notably, curcumin interferes with the binding of HBV to the hepatocyte plasma membrane, thereby inhibiting viral entry, although the precise mechanism remains unclear.[32,33] Among its antiviral properties, curcumin has shown a more pronounced inhibitory effect on HBV infection. It reduces viral load by disrupting HBV replication, suppressing viral protein expression, and modulating host immune responses to mitigate inflammation and oxidative stress.[34] Covalently closed circular DNA (cccDNA), a key template for HBV replication and mRNA synthesis, serves as a major obstacle to HBV eradication. In HBV-infected HepG2.2.15 cells, curcumin (20 μmol/L) induced deacetylation of histone H3/H4 bound to cccDNA, destabilizing the cccDNA strand and leading to the suppression of HBV mRNA transcription and viral protein expression. This effect was associated with a dose-dependent reduction in HBsAg and HBeAg levels, suggesting curcumin's role in HBV prevention and treatment.[35] Furthermore, curcumin exerts inhibitory effects at different stages of the HBV life cycle. During the early and replicative phases, curcumin significantly reduces viral load, HBeAg, and HBV DNA levels. A dose-dependent study demonstrated that curcumin (10, 20, and 30 μM) effectively decreased HBV viral load, with the most pronounced effect at 30 μM. Additionally, in the early stages of viral transport, curcumin modulates sodium taurocholate cotransporting polypeptide (NTCP) receptors, thereby preventing HBV attachment and internalization into hepatocytes.[36]

Drug-Induced Liver Injury

The liver plays a central role in drug metabolism and is therefore a major target for drug-induced injury.[37] Studies have demonstrated that curcumin exerts hepatoprotective effects in various models of liver injury. Thioacetamide (TAA), a classical hepatotoxin known to induce fulminant hepatic failure, causes degenerative changes in liver cells, including vacuolization, fibrosis, inflammation, and moderate focal necrosis. However, curcumin treatment (50 mg/kg for 2 weeks) significantly reversed these pathological alterations in a rat model. In the TAA and curcumin co-treated group, markers of hepatic injury—including ALT, AST, ALP, and lactate dehydrogenase (LDH)—were significantly reduced, while indicators of hepatic function and protein synthesis, such as albumin and total protein, were markedly increased. Additionally, curcumin inhibited TNF-alpha expression, thereby exerting anti-inflammatory effects and preventing hepatic fibrosis progression.[38] Aflatoxins, highly toxic mycotoxins commonly found in food, pose a significant risk for liver injury, with aflatoxin B1 (AFB1) being the most carcinogenic and a major risk factor for hepatocellular carcinoma in the Asia-Pacific region.[3] Curcumin (200 mg/kg for 30 days) was found to counteract AFB1-induced hepatocyte pyroptosis, likely through modulation of the NLRP3/Caspase-1/GSDMD pathway and restoration of the Nrf2 signaling pathway. Furthermore, curcumin mitigated AFB1-induced hepatotoxicity and oxidative stress by scavenging MDA accumulation and activating Nrf2 signaling, thereby enhancing antioxidant capacity and glutathione S-transferase (GST)-mediated Phase II detoxification.[39] Isoniazid, a first-line anti-tuberculosis drug, is associated with hepatotoxicity, which significantly limits its clinical application. Studies have shown that curcumin (2 or 5 μmol/L) alleviates isoniazid-induced vacuolization and inflammatory responses in liver cells. In both in vitro (L-02 hepatocyte cells) and in vivo (BALB/c mice) models, curcumin reduced isoniazid-induced hepatotoxicity by activating the SIRT1/PGC-1alpha/NRF1 pathway, decreasing oxidative stress and inflammation, and thereby attenuating hepatic damage.[40] Moreover, curcumin (1, 2.5, and 5 mg/kg/day for 10 days) was effective in mitigating liver damage caused by the agricultural insecticide cypermethrin (Cyp). In a Cyp-induced hepatotoxicity rat model, curcumin reversed Cyp-induced ROS accumulation, decreased oxidative stress by downregulating ROS levels, and reduced hepatic toxicity by decreasing inflammatory cytokine expression and suppressing autophagy.[41]

Hepatic Fibrosis

Hepatic fibrosis (HF) is a reversible compensatory response to liver injury and tissue repair following inflammation induced by various pathogenic factors. It is characterized by the excessive accumulation of ECM and persistent chronic inflammation. The regulation of ECM is influenced by multiple cellular pathways, including hepatocytes, liver sinusoidal endothelial cells (LSECs), hepatic stellate cells (HSCs), and Kupffer cells (KCs).[42] In a rat model of TAA-induced hepatic fibrosis, curcumin (400 mg/kg for 4 weeks) significantly downregulated beta-catenin protein expression and activity in HSCs, thereby inhibiting HSC activation and preventing hepatic fibrosis.[43] Additionally, curcumin (100, 200, and 300 mg/kg for 8 weeks) was found to accelerate HSC senescence via activation of the PPARgamma/P53 signaling pathway, thereby reducing ECM accumulation and chronic inflammation.[44] RhoA, a key downstream molecule of the CXCL12/CXCR4 axis, is closely linked to HSC activation, migration, and adhesion. Curcumin (50, 100, and 200 mg/kg for 8 weeks) inhibited HSC activation and migration by suppressing the CXCL12/CXCR4 bioaxis and its downstream RhoA/ROCK signaling pathway.[45] Furthermore, both in vitro and in vivo studies demonstrated that curcumin (400 mg/kg for 4 weeks) inhibited the hepatic fibrosis process by targeting the p38MAPK pathway, thereby downregulating the expression of methionine adenosyltransferase 2B in HSCs.[46]

Beyond its direct effects on HSCs, curcumin's anti-inflammatory and antioxidant activities also contribute to the reversal of hepatic fibrosis. In a carbon tetrachloride (CCl_4)-induced rat model of liver fibrosis, curcumin (200 mg/kg for 6 weeks) reduced Gr1hi monocyte recruitment by downregulating MCP-1 expression. This, in turn, indirectly suppressed the expression of pro-inflammatory and pro-fibrotic cytokines, including TNF-alpha, IL-1beta, and TGF-beta.[47] Additionally, Abo-Zaid et al reported that curcumin (150, 200, and 250 mg/kg for 6 weeks) exerted anti-inflammatory effects by upregulating IL-10, leading to the downregulation of TNF-alpha, IL-6, and TGF-beta, which ultimately improved hepatic histology.[48] In a bile duct ligation (BDL)-induced fibrosis model, curcumin (100 mg/kg daily for 28 days) significantly decreased oxidative stress by downregulating Rac1-guanosine triphosphate, Rho-related C3 botulinum toxin substrate, and NOX1, thereby alleviating liver injury and exerting antifibrotic effects.[49]

Moreover, intrahepatic neovascularization and the formation of abnormal hepatic vasculature are closely linked to the progression of fibrosis. In a CCl_4-induced rat liver fibrosis model, curcumin (200 mg/kg for 6 weeks) attenuated liver injury by inhibiting pro-angiogenic factors, including HIF-1alpha, VEGFR-1, placental growth factor, and COX-2, thus interfering with angiogenesis and hepatic sinusoidal capillarization.[50] HIF has been identified as a critical regulator of angiogenesis, inflammation, and metabolism.[51] Among its family members, HIF-1alpha is particularly involved in promoting angiogenesis and inflammatory responses. In a rat model, curcumin (1200 mg/kg for 6 weeks) was found to inhibit hepatic fibrosis by targeting the ERK/HIF-1alpha pathway, thereby suppressing the downstream expression of fibrosis-related genes such as collagen type III and alpha-smooth muscle actin.[52]

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is one of the most prevalent gastrointestinal malignancies worldwide, accounting for approximately 830,000 deaths annually. It ranks as the third leading cause of cancer-related mortality, following lung and colorectal cancers, and represents the most common subtype of primary liver cancer.[53] Given the multifactorial nature of HCC progression and the limited efficacy of current therapeutic strategies, bioactive compounds with diverse pharmacological properties have garnered significant attention.[54] Curcumin has been shown to interfere with HCC progression primarily by modulating key oncogenic signaling pathways, including the PI3K/AKT and Wnt/beta-catenin pathways, both of which are closely associated with cell growth, proliferation, and tumor progression.[55,56] Using the H22 murine HCC cell line, Pan et al demonstrated that curcumin (40 and 80 μM) effectively inhibited the PI3K/AKT pathway, leading to downregulation of vascular endothelial growth factor (VEGF) expression and suppression of HCC cell proliferation.[57] This was corroborated by another study in which curcumin (20 μM) inhibited the growth and induced apoptosis of liver cancer stem cells (LCSCs) by suppressing the PI3K/AKT/mTOR pathway. Mechanistically, inhibition of the PI3K/AKT/mTOR axis resulted in increased expression of pro-apoptotic proteins caspase-3, caspase-9, and Bax, while reducing the expression of the anti-apoptotic protein Bcl-2, thereby accelerating apoptotic events in LCSCs.[58] Additionally, Bai et al reported that curcumin (20, 40, and 60 μM) suppressed PI3K/AKT signaling by downregulating BCLAF1 in a time- and concentration-dependent manner. This inhibition disrupted the PI3K/AKT/GSK-3beta signaling cascade, triggering mitochondrial apoptotic pathways in HCC cells.[59] In BEL-7402 and QGY-7703 hCC cell lines, curcumin (80 μM) effectively suppressed tumor cell growth and proliferation by inhibiting beta-catenin activity and downregulating the Wnt signaling pathway.[60] Furthermore, curcumin (50 μM) was found to activate p38 MAPK in Huh-7 cells, subsequently inducing the synthesis of FasL, which facilitated apoptosis.[61] Another important molecular target of curcumin in HCC treatment is NF-κB. In cancer stem-like cells (CSCs), curcumin (25 μM for 3 days) promoted apoptosis by inhibiting the NF-κB signaling pathway and downregulating the expression of histone deacetylases.[62] Moreover, in a streptozotocin (STZ) + HFD-induced NASH-HCC mouse model, curcumin (100 mg/kg/day for 4 weeks) prevented the transition from NASH to HCC by decreasing oxidative stress and blood glucose levels. This effect was achieved via downregulation of HMGB1 and inhibition of NF-κB nuclear translocation[63] Figure 2.

Combination of Drugs

In the treatment of chronic liver diseases, the use of single drugs often presents certain limitations, while combination therapies with other substances have the potential to significantly enhance therapeutic outcomes. Studies have confirmed that curcumin, when combined with other compounds or drugs (such as immunomodulators, glucose, or anticancer agents), can produce synergistic effects and improve treatment efficacy. For example, the combination of salidroside and curcumin has been shown to inhibit the inflammatory response, enhance antioxidant capacity, and alleviate liver injury caused by a high-fat diet.[64] The curcumin-berberine combination exerts anticancer effects by regulating the miR-221/SOX11 axis and activating pro-apoptotic proteins, thereby inhibiting the growth and proliferation of hepatocellular carcinoma cells.[65] Kim et al demonstrated that combining curcumin with glucose significantly alkalized the tumor microenvironment, which in turn inhibited the proliferation and migration of hepatocellular carcinoma cells, exerting potent anticancer effects.[66] In conclusion, combination therapy offers a more comprehensive approach, improving pathological conditions while minimizing the side effects of individual drugs. (see Table 1 for details).

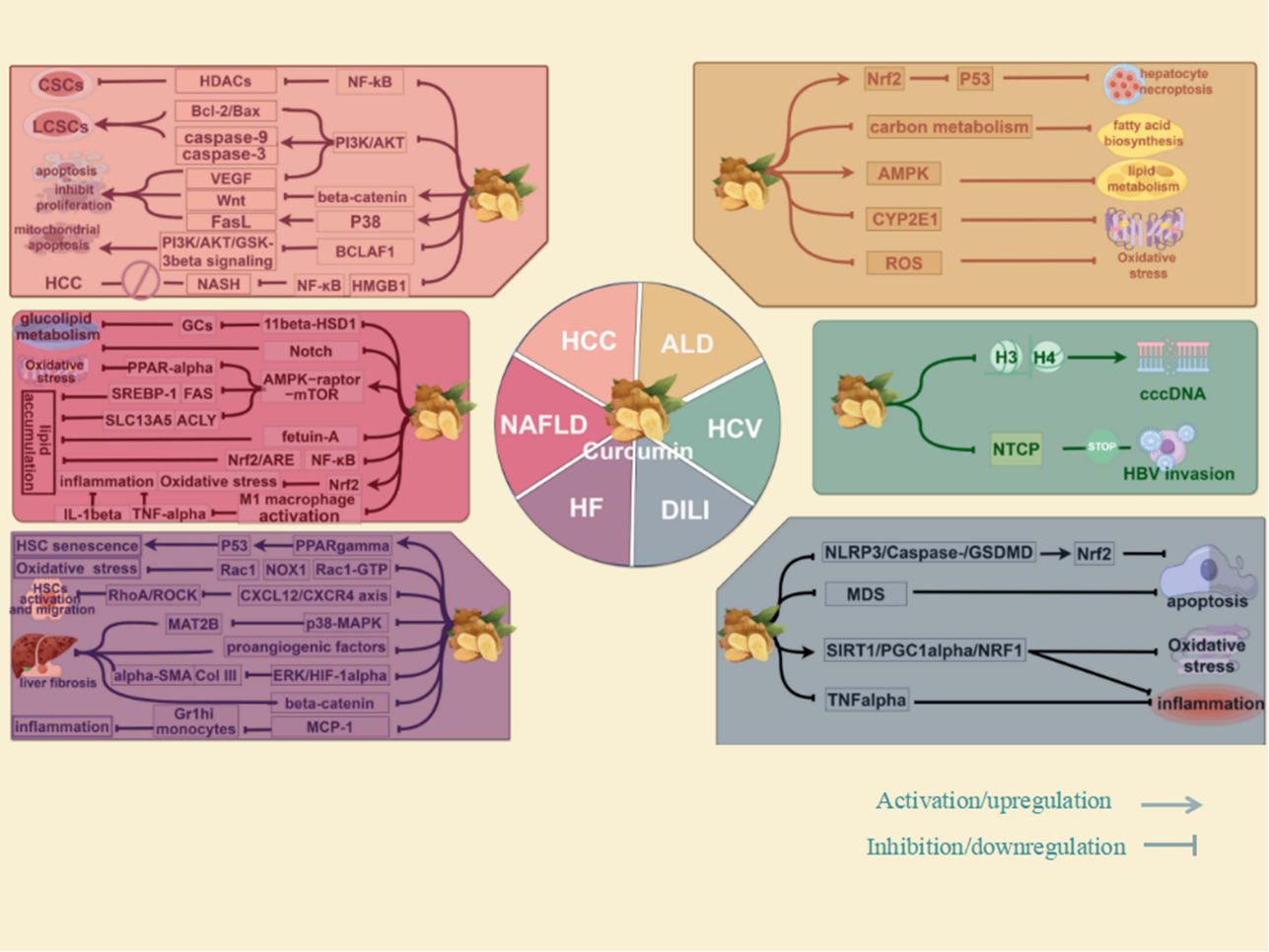

Figure 2 Mechanisms of Curcumin in the Treatment of Chronic Liver Diseases.

Conclusion

In summary, curcumin, as a dietary supplement, exerts its therapeutic potential in chronic liver diseases by directly or indirectly modulating various enzymes, growth factors, inflammatory cytokines, and transcription factors at the molecular level. Through its antioxidative, anti-inflammatory, hepatoprotective, glucose and lipid metabolism-regulating, antifibrotic, antiviral, and bidirectional autophagy – and apoptosis-modulating properties, curcumin contributes to liver disease prevention and treatment. Additionally, as a dietary ingredient, a single oral dose of 0.5–12 g of curcumin has been shown to be safe and well-tolerated.[84] Thus, curcumin is widely available in conventional food products, including dietary nutrients, flavoring agents, and vitamin supplements.

Despite its therapeutic potential, curcumin's clinical application is often hindered by its poor water solubility, rapid metabolism, and short half-life.[85] However, advancements in drug delivery systems have gradually addressed these challenges. Various carrier systems, such as microencapsulation, phospholipid complex embedding, raw material compounding, and nano-delivery technologies, have significantly improved curcumin's bioavailability. Notably, micronized curcumin formulations, especially liquid micellar preparations, have demonstrated enhanced absorption without causing significant hepatic or renal toxicity.[86] Additionally, structural modifications—including alterations to the diketone moiety, carbonyl adsorption, and heterocyclic junctions—have further improved curcumin's pharmacokinetic properties.[87,88]

Furthermore, curcumin analogues (eg, tetrahydrocurcumin [THC], hexahydrocurcumin [HHC], octahydrocurcumin [OHC], and NL13[89]) exhibit superior therapeutic potential due to their structural optimizations. For instance, THC has

Table 1 Interaction of Curcumin with Various Drugs and/or Nutraceutical

Interaction		Subject	Mechanisms	Clinical/Pre-Clinical Outcome	Reference
Curcumin	+Salidroside	Rat	↓TG and FFA, ↓TNF-alpha and IL-1, FINS, ↓FBG, HOMA-IR, MDA, ACCase, pACCase, CoA; ↑SOD, AMPKand CPT-1	Amelioration of hepatic injury and lipid deposition in a rat model of NAFLD induced by a high-fat diet	[64]
Curcumin	+ Berberine	HEPG2 and Huh7	↓miR-221; ↑SOX11, caspase-3/9	Combined action of CUR-BBR inhibits growth and induces apoptosis in HCC cells	[65]
Taurine	+ Curcumin	Rat	↓MDA; ↑CAT, GST, GPx, SOD	Mitigation of BPA-induced liver injury	[67]
Curcumin	+Berberine	Rat	↓TG, TC, LDL-c and FFA, ↓LDL-c, ALT, AST, ALP, MDA, LSP, ↓SREBP-1c, pERK, TNF-alpha and pJNK; ↑GSH-Px	Enhanced clinical efficacy of combined applications in the treatment of NAFLD by improving oxidative stress, hepatic inflammation and lipid metabolism	[68]
Curcumin	+Oxaliplatin	Mice	↓AST, MDA, ↓CXCL1, CXCL2 and MCP-1, ↓PAI-1; ↑Nrf2, ↑SOD, CAT and GSH, ↑HO-1 and NQO1	Curcumin attenuates OXA-induced hepatic pathology and splenomegaly	[69]
Curcumin	+ Resveratrol	Mouse and HepG2	↓HDL and LDL, TG and TCH, ALT, ↓TNF-alpha, IL-6, IL-1beta, and COX-2, ↓ICAM-1, VCAM-1 and MCP-1, ↓F4/80, ↓Phosphorylation level of ERK, alpha-SMA, COL-I, COL-IV and TGF-beta	Synergistic inhibition of lipid accumulation, hepatic injury, hepatic inflammation and fibrosis in HFD-induced NAFLD mouse model	[70]
Curcumin	+Resveratrol	HepG2	↓tumor growth; ↑ROS, caspase-3	Synergistic inhibition of liver cancer	[71]
Curcumin	+Ursodexycholic acid	Rat	↓TG and HDL-C, ↓Fatty degeneration, cellular necrosis, edema and immune cell infiltration, p53 and caspase III, ↓iNOS, NO, SGPT, SGOT; ↑bcl-2, TAC, GSH-Px and SOD	Synergistic amelioration of NAFLD-induced apoptosis, steatosis, and hepatic injury and inflammatory response	[72]
Curcumin	+ Sorafenib	Mice	↓ALT, MDA, AFP, Vim, ↓IL-1beta, NF-κB, p-JAK1/2 and p-STAT3, ↓HIF-1alpha, ↓LDH, TG, FASN, CPT1A, ↓protein phosphorylation of AKT (Ser473); ↑CD4+ T cells, E-Cad, IL-4, ↑HDL-C, apoA1, p53	Curcumin enhances the hepatocellular carcinoma efficacy of sorafenib by activating immune function, downregulating EMT, and modulating metabolic disorders	[73]
Curcumin	+ Dimethyl fumarate	Rats	↓ALT and AST, MDA, ↓MPO, TNF-alpha; ↑Nrf2/HO-1 signaling pathway, GSH, SOD and TAC	Both synergistically enhance anti-inflammatory and antioxidant effects and attenuate hepatic ischemia/reperfusion injury	[74]
Curcumin	+ N-n-butyl haloperidol iodide	SMMC-7721 and Hep3B	↓EZH2, ↓cell proliferation, Bcl-2 and BclxL, EZH2, H3K27me3, ↓Wnt/beta-catenin, ↓EZH2-H19; ↑Bax, Axin2	Synergistic inhibition of malignant proliferation and induction of apoptosis in hepatocellular carcinoma	[75]
Curcumin	+ Resveratrol	HepG2	↓area of fat droplets, ↓LDL-C, TG and TC, ↓PI3K, AKT, mTOR and STAT3, ↓HIF-1	Synergistic treatment of steatosis in MAFLD	[76]
Curcumin	+Sodium pentaborate pentahydrate +piperine	HepG2 and Hep3B cells	↓growth of HCC cells	Synergistically inhibits HCC cells growth and promotes apoptosis	[77]

(*Continued*)

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Table 1 (Continued).

Interaction		Subject	Mechanisms	Clinical/Pre-Clinical Outcome	Reference
Curcumin	+Ethanol	Rats	↑CD8+ T cell infiltration, CD8 +/Treg ratio; ↓PD-L1, STAT3, p-p65	Enhanced anticancer effect of immuno-ethanol ablation	[78]
Curcumin	+Lenvatinib	HCC cell lines	↓proliferation, invasion and colony of HCC cells, EGFR, PI3K-AKT Pathway; ↑ROS	Curcumin reverses Lenvatinib resistance in HCC	[79]
Curcumin	+Doxorubicin	SMMC 7721 cells	↑cytotoxicity and cell apoptosis in SMMC 7721 cells; ↓VEGF	Synergistic inhibition of liver cancer progression	[80]
Curcumin	+ Capsaicin	Mice and HepG2, LX-2, H22 (mouse hepatoma cell line), and mHSCs (mouse HSCs)	↓ECM, EMT, P-gp, the activation of HSCs, vascular proliferation	Synergistic inhibition aHSC-induced drug resistance and metastasis	[81]
Curcumin	+Astragali Polysaccharide	Mice	↓tumor growth; ↑NG2, the Morphological Structure of Tumor Vessels	Synergistically improves tumor vascular morphology and structure, induces tumor vascular normalization, and inhibits hepatocellular carcinoma growth	[82]
Curcumin	+5-fluorouracil	Bel-7402 and HepG2 cells, Mice	↑apoptosis, G2/M cell cycle arrest, regulation of intestinal flora; ↓tumor growth, PI3K/AKT signalling pathway,	Synergistic enhancement of anticancer effect	[83]

been reported to aid in breast cancer treatment,[90] improve cardiac function,[91] and alleviate retinal diseases.[92] OHC possesses potent anti-inflammatory[93] and antitumor[94] activities, whereas HHC has demonstrated neuroprotective properties in cognitive disorders[95] and ischemia-reperfusion injury. In addition, given the limitations of monotherapy, researchers are actively exploring combination strategies involving curcumin and other pharmacological agents to enhance efficacy in chronic liver diseases, with promising preliminary results.

In conclusion, curcumin, as a natural multifunctional therapeutic compound, holds significant potential for clinical application in chronic liver diseases. However, further large-scale clinical trials and dose optimization studies are essential to validate its efficacy and safety in the prevention and treatment of chronic liver diseases.

Abbreviations

ACCase, acetyl-CoA carboxylase; AKT, Protein Kinase B; ALP, Alkaline phosphatase; ALT, Alanine transaminase; AMPK, AMP-activated protein kinase; ARE, Antioxidant response element; AST, Aspartate aminotransferase; Bax, BCL2-Associated X; Bcl, B-cell lymphoma; Bcl-2, B-cell lymphoma 2; CAT, Catalase; COL-I, Collagen Type I; COL-IV, Collagen Type IV; COX-2, Cyclooxygenase-2; CPT-1, Carnitine palmitoyltransferase 1; CPT1A, Carnitine palmitoyltransferase 1A; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; ERK, Extracellular signal-regulated kinase; EZH2, Enhancer of Zeste Homolog-2; EZH2-H19, Enhancer of zeste homolog 2-H19; EMT, Epithelial−mesenchymal transition; EGFR, Epidermal growth factor receptor; FAS(FASN), Fatty acid synthase; FasL, Factor-related Apoptosis ligand; FBG, Fasting blood glucose; FFA, Free fatty acid; FINS, Fasting insulin; GGT, Gamma Glutamyl Transferase; GSDMD, Gasdermin D; GSH, Glutathione; GSH-Px(GPx), Glutathione peroxidase; GSK-3beta, Glycogen synthase kinase-3 beta; H3K27me3, Trimethylated of H3 on lysine 27; HBeAg, Hepatitis Be antigen; HBsAg, Hepatitis B surface antigen; HDL-C, High density lipoprotein cholesterol; HIF-1, Hypoxia-inducible factor-1; HIF-1alpha, Hypoxia-inducible factor-1alpha; HMGB1, High mobility group box 1 protein; HO-1, Haeme oxygenase-1; HOMA-IR, Homeostasis model assessment of insulin resistance; ICAM, Intercellular cell adhesion molecule; IFN-gamma, Interferon-gamma; IL-1, Interleukin-1; IL-1beta, Interleukin-1beta; IL-6, Interleukin-6;

JNK, c-Jun N-terminal kinase; LDL, Low-Density Lipoprotein; LDL-c, Low-Density Lipoprotein Cholesterol; LSP, Lipopolysaccharide; MAPK, Mitogen-activated protein kinase; MCP-1, Monocyte chemoattractant protein-1; MDA, Malondialdehyde; MPO, Myeloperoxidase; NF-κB, Nuclear factor kappa B; NLRP3, Nucleotide-binding oligomerization domain (NOD)-like receptor protein 3; NOX1, NADPH oxidase 1; NQO1, NAD(P)H:quinine oxidoreductase 1; NRF1, Nuclear factor erythroid-derived 2-related factor 1; Nrf2, Nuclear factor erythroid 2-related factor 2; NG2, Neural/glial antigen 2; p53, Tumor protein P53; pACCase, Phosphorylated acetyl-CoA carboxylase; PAI-1, Plasminogen activator inhibitor-1; PGC-1alpha, Peroxisome proliferator-activated receptor gamma coactivator 1 alpha; P-gp, P-glycoprotein; PI3K, Phosphoinositide 3-kinase; PPAR-alpha, Peroxisome proliferator-activated receptor-alpha; PPAR-gamma, Peroxisome proliferator-activated receptor-gamma; ROCK, Rho-associated coiled-coil-containing protein kinase; ROS, Reactive oxygen species; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; SIRT1, Silent information regulator 1; SLC13A5, Cytoplasmic citrate flux, mediated by plasma membrane citrate transporter; SOD, Superoxide dismutase; SOX11, MiR-221/SRY-box transcription factor 11; SREBP-1, Sterol regulatory element-binding protein 1; STAT3, Signal transducers and activators of transcription 3; TAC, Total antioxidant capacity; TC, Total cholesterol; TG, Triglyceride; TGF-beta, Transforming growth factor-beta; TNF-alpha, Tumor necrosis factor alpha; VCAM-1, Vascular cell adhesion molecule-1.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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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