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Review Article

Therapeutic Applications and Pharmacological Actions of Luteolin in Liver Diseases

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Abstract

Luteolin is a dietary flavonoid widely distributed in fruits and vegetables. It has attracted substantial preclinical interest due to its pleiotropic hepatoprotective effects against hepatic steatosis, inflammation, fibrosis, and hepatocellular carcinoma. By reviewing data from *in vitro* and *in vivo* studies, this review comprehensively synthesizes the full spectrum of liver-directed pharmacology of luteolin, covering metabolic and toxic liver injury, fibrosis, cancer, and viral hepatitis, while critically mapping each mechanism to specific disease contexts and systematically identifying the key challenges limiting its clinical translation. The underlying mechanisms of luteolin action involve activation of Nrf2-mediated antioxidant defense, suppression of NF-κB- and NLRP3-driven inflammatory responses, inhibition of hepatic stellate cell activation via the TGF-β/Smad and STAT3 pathways, and regulation of metabolic homeostasis through liver X receptor (LXR)/SREBP-1c and AMPK signaling. Despite well-characterized mechanisms in preclinical models, several critical gaps hinder its clinical translation: (1) Rigorous randomized controlled trials in well-defined patient populations are scarce, with only one combination supplement study reported. (2) The relative contribution of luteolin metabolites to its overall bioactivity remains poorly understood, even though derivatives such as luteolin-7-diglucuronide exhibit distinct pharmacological properties. Cell-type-specific delivery systems, which show promise in preclinical fibrosis and cancer models, have not been evaluated clinically. (3) Systematic studies on the synergistic effects of luteolin with standard-of-care drugs remain largely exploratory. Overall, luteolin is a promising multi-target nutraceutical for liver diseases, and its clinical translation requires optimized delivery strategies, investigation of metabolite activity, and well-designed human clinical trials.

Introduction

Liver diseases represent a major and growing global health burden, with etiologies ranging from metabolic dysfunction and viral infections to toxin exposure, autoimmune processes, and malignancy. Despite significant therapeutic advances in areas such as antiviral therapy for hepatitis and immune checkpoint inhibitors for hepatocellular carcinoma (HCC), many liver conditions—particularly metabolic dysfunction-associated steatotic liver disease (MASLD), advanced fibrosis, and drug-induced liver injury (DILI)—remain challenging to manage. For these diseases, therapeutic options are often limited, nonspecific, or associated with significant adverse effects, and patients frequently progress to cirrhosis, liver failure, or HCC. This persistent unmet clinical need underscores the urgency of identifying novel, effective, and safe therapeutic agents.[1–4]

Natural products have historically been a rich source of pharmacologically active compounds, and dietary flavonoids are receiving increasing attention. Luteolin (3′,4′,5,7-tetrahydroxyflavone), a common flavone found in vegetables, fruits, and medicinal herbs, has emerged as a promising multi-target bioactive molecule. A growing body of preclinical evidence demonstrates that luteolin possesses hepatoprotective, anti-inflammatory, anti-fibrotic, and anti-tumor activities, primarily through the modulation of oxidative stress, inflammatory signaling, metabolic pathways, and cell death mechanisms.

However, despite this compelling body of evidence, the translation of luteolin from bench to bedside is hindered by several critical research gaps. First, much of the mechanistic understanding remains fragmented, with studies often focusing on isolated pathways in disparate models, obscuring a holistic view of its multi-target actions in the liver. Second, its clinical potential is severely limited by unfavorable pharmacokinetic properties, particularly

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poor aqueous solubility, extensive first-pass metabolism, and low oral bioavailability; the lack of clinically viable, targeted delivery systems remains a major barrier. Third, rigorous human clinical trials are extremely scarce. The majority of evidence is derived from *in vitro* and animal models, leaving its true efficacy, optimal dosing, and long-term safety in humans inadequately defined.

This review aims to address these gaps by pursuing three specific objectives: (1) to provide a comprehensive, integrative, and up-to-date synthesis of the pharmacological actions of luteolin across the full spectrum of liver diseases, from steatosis and acute injury to fibrosis and HCC; (2) to critically analyze the molecular mechanisms and signaling networks through which luteolin exerts its effects, with a focus on its coordinated antioxidant, anti-inflammatory, and metabolic regulation; and (3) to systematically identify the key challenges limiting its clinical translation, primarily bioavailability and delivery, and to highlight emerging strategies, such as cell-specific delivery, nanocarrier systems, and rational combination therapies, that are poised to overcome these hurdles. By consolidating current knowledge, clarifying unresolved questions, and defining a forward-looking research agenda, this review will chart a path from promising preclinical data to clinical application of luteolin in liver health and disease.

Liver diseases targeted by luteolin

Non-alcoholic fatty liver disease (NAFLD)/MASLD

NAFLD, recently redefined as MASLD to emphasize its metabolic underpinnings, is characterized by hepatic steatosis in the absence of significant alcohol consumption. It ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), which can progress to fibrosis, cirrhosis, and HCC.[5–8]

Luteolin has shown considerable efficacy in ameliorating hepatic steatosis, inflammation, and fibrosis in various NAFLD/MASLD models. In a rat methionine-choline-deficient diet (MCDD) NASH model, luteolin protected against inflammation, fibrosis, and hepatocarcinogenesis.[9] In high-fat diet (HFD)-induced obese mice, luteolin treatment reduced body weight, improved insulin sensitivity, and decreased hepatic lipid accumulation.[10] In an MCDD-induced NASH mouse model, luteolin supplementation alleviated hepatic lipid deposition, liver dysfunction, and oxidative stress, accompanied by significant alterations in the serum metabolome and gut microbiome. Specifically, luteolin modulated metabolites such as thiamine and carnitine derivatives and increased beneficial genera such as *Erysipelatoclostridium* and *Pseudomonas* while decreasing *Faecalibaculum*.[11]

Additionally, luteolin protects against NAFLD associated with insulin resistance by regulating the PI3K/AKT/FoxO1 pathway. In a diabetic rat model induced by HFD and streptozotocin, luteolin-loaded zinc oxide nanoparticles effectively reduced hyperglycemia, hyperinsulinemia, insulin resistance, and hepatic steatosis.[12] In a high-carbohydrate diet/HFD–induced NASH rat model, luteolin exerted protective effects by targeting pro-inflammatory interleukin-1 and interleukin-18 (IL-18) pathways and exerting antioxidant activity.[13]

Given the prominence of the gut-liver axis in NAFLD pathogenesis, luteolin was shown to alleviate NAFLD in HFD-fed rats by restoring intestinal mucosal barrier integrity and correcting gut microbiota imbalance. It enhanced tight junction protein expression, reduced intestinal permeability to fluorescein isothiocyanate-dextran (FD4), and inhibited the hepatic Toll-like receptor 4 (TLR4) signaling pathway, thereby lowering pro-inflammatory factors.[14] Another study confirmed that the anti-inflammatory effect of luteolin in preventing progression from simple steatosis to NASH is associated with beneficial changes in gut microbiota, increased zonula occludens-1 abundance, reduced intestinal permeability and plasma lipopolysaccharide (LPS) levels, and inhibition of the TLR4/NF-κB pathway in HFD-fed rats.[15] Luteolin also improved liver lipid metabolism and regulated gut microbiota in obese rats with polycystic ovary syndrome.[16]

Luteolin was also found to improve NAFLD in db/db mice by competitively binding to the ligand-binding domain of LXRs, thereby suppressing LXR activation induced by agonists or high glucose, leading to downregulation of SREBP-1c and reduced hepatic triglyceride (TG) accumulation.[17] Its glycosylated form, luteolin-7-glucoside, induced Ppar-α and its target gene carnitine palmitoyltransferase 1 (*Cpt-1*) in rat liver while repressing HMG-CoA reductase expression and activity at high concentrations, contributing to an improved plasma lipid profile.[18] In a high-fructose diet–induced metabolic syndrome rat model, luteolin ameliorated cardiovascular and hepatic changes by reducing oxidative stress, inflammation, and histological damage in heart and liver tissues.[19]

As early as 2019, a randomized, double-blind, placebo-controlled human study demonstrated that a supplement containing luteolin and chlorogenic acid (Altilix®) improved hepatic and cardiometabolic parameters in subjects with metabolic syndrome over six months, including reduced fatty liver index, liver enzymes, and carotid intima-media thickness.[20] More recently, luteolin was shown to relieve NAFLD/MASLD in HFD-fed rats by modulating the AdipoR1/AMPK/PPARγ signaling pathway, improving metabolic parameters, reducing oxidative stress and inflammation, and attenuating hepatic steatosis.[21] Furthermore, dietary supplementation with luteolin before fatty liver formation in HFD-fed mice improved hepatic steatosis not by affecting body weight but by inhibiting visceral adipose tissue lipolysis. Luteolin inhibited serotonin-induced lipolysis in adipocytes by binding to the 5-HT receptor HTR2B, thereby blocking the Ca^{2+}-PKG cascade and SIRT1/FoxO1/AMPKα signaling.[22]

In summary, luteolin effectively improves hepatic steatosis, inflammation, and fibrosis in NAFLD/MASLD models by modulating metabolic pathways, gut microbiota, and inflammatory signaling. It also shows protective effects in human studies, improving liver and cardiometabolic parameters.

Alcoholic liver disease (ALD)

ALD encompasses a spectrum of liver injuries from simple steatosis to alcoholic hepatitis, fibrosis, cirrhosis, and HCC, driven by chronic and excessive alcohol consumption.[23] Its pathogenesis involves acetaldehyde accumulation, reactive oxygen species (ROS), and pro-inflammatory factors during alcohol metabolism.[24,25]

Luteolin exhibits protective effects against ethanol-induced liver injury. In a chronic-and-binge ethanol feeding mouse model, luteolin reduced serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, hepatic TG accumulation, oxidative stress, and expression of lipogenic genes (*Srebp-1c*, fatty acid synthase (*Fasn*), acetyl-CoA carboxylase (*Acc*), *Scd1*).[26] Recent studies have elucidated that luteolin protects against alcoholic liver injury by restoring nuclear factor erythroid 2–related factor 2 (Nrf2) stability, thereby suppressing nuclear accumulation of acyl-CoA synthetase short-chain family member 2 and subsequent histone H3 acetylation, leading to reduced hepatic lipogenesis.[27] Additionally, luteolin, in combination with gallic acid extracted from *Luffa acutangula* var. *amara* fruit pericarp, showed hepatoprotective effects against alcohol-induced toxicity in a chronic alcohol-induced hepatotoxic-

ity rat model.[28] Luteolin also improves lipid profiles and increases liver glycogen content through modulation of glycogen synthase kinase-3 in healthy rats.[29] In a diethylnitrosamine (DEN)-initiated and alcohol-promoted preneoplastic lesion mouse model, dietary luteolin supplementation significantly reduced hepatic inflammatory foci, steatosis, and preneoplastic lesions, an effect associated with increased sirtuin 1 (Sirt1) activity.[30]

Luteolin encapsulated in gelatin–finger citron polysaccharide composite nanoparticles demonstrated enhanced aqueous solubility and bioavailability and significantly ameliorated symptoms in an acute ALD mouse model by reducing lipid accumulation and oxidative stress and inhibiting the NF-κB pathway.[31]

Thus, luteolin protects against alcohol-induced liver injury by reducing oxidative stress, lipid accumulation, and inflammation, with enhanced efficacy via nanoparticle delivery.

DILI/toxin-induced liver injury

DILI is a common cause of acute liver failure.[32–34] Luteolin has demonstrated broad-spectrum protective effects against liver damage induced by various hepatotoxins.

Luteolin protected mice against CCl_4-induced hepatotoxicity in a dose- and time-dependent manner by reducing serum ALT and AST, alleviating oxidative stress, improving antioxidant status, and promoting liver regeneration, possibly through modulation of metallothioneins and metals.[35,36] Notably, luteolin attenuated CCl_4-induced hepatic injury in mice by inhibiting ferroptosis, a regulated cell death driven by lipid peroxidation, via upregulation of solute carrier family 7 member 11 (Slc7a11).[37] Its glycoside, luteolin-7-glucoside, also showed protective effects against CCl_4 injury in rats, attributed to its antioxidant properties.[38] Furthermore, metformin and luteolin in combination showed synergistic protection against CCl_4-induced hepatotoxicity in rats, involving enhanced antioxidant, anti-inflammatory, and anti-apoptotic effects, and upregulation of the Nrf2/heme oxygenase-1 (HO-1) pathway.[39]

Against acetaminophen (APAP) overdose, luteolin protected L02 liver cells by reducing oxidative stress (decreasing MDA, increasing glutathione (GSH) and SOD) and inhibiting apoptosis via modulation of Bcl-2/Bax and caspase-3.[40] *In vivo*, luteolin administration protected mice against APAP-induced acute liver failure by reducing serum ALT, AST, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and MDA levels, restoring antioxidant enzymes (SOD, GSH, GSH-Px), and downregulating inducible nitric oxide synthase (iNOS), NF-κB, and endoplasmic reticulum (ER) stress markers.[41] Luteolin–β-cyclodextrin metal-organic framework significantly improved dissolution, antioxidant activity, and bioavailability (□4-fold in healthy rats and □11-fold in APAP-injured rats), exhibiting superior hepatoprotective effects compared to raw luteolin.[42] Further investigation revealed that its protective mechanism involves regulating bile acid metabolism and restoring gut microbiota balance disrupted by APAP overdose.[43] Luteolin carried by dipotassium glycyrrhizinate micelle nanomaterials demonstrated strong effects against APAP-induced hepatotoxicity by inhibiting high-mobility group box 1 (HMGB1) signaling and suppressing oxidative stress.[44]

Luteolin protects against diclofenac-induced gastroenterohepatic damage exacerbated by sodium fluoride co-exposure,[45] mitigates tamoxifen-associated fatty liver and cognitive impairment in rats by modulating β-catenin and reducing inflammation,[46] and protects against tunicamycin-induced ER stress in the liver via Nrf2-dependent sestrin 2 induction based on studies using hepatocyte-derived cells, primary hepatocytes, and mouse models.[47]

Luteolin pretreatment alleviated methamphetamine (METH)-induced rat liver damage, involving modulation of oxidative phosphorylation, cytochrome P450, and certain signaling pathways, as revealed by RNA sequencing analysis.[48] A later study elucidated that luteolin alleviates METH-induced hepatic apoptosis, autophagy, and inflammation primarily by repressing the p53 pathway in rats.[49] Luteolin also ameliorates methotrexate-induced hepato-renal toxicity via its antioxidative, anti-inflammatory, and anti-apoptotic effects in rats and showed protective effects against pentetrazol-induced seizure-associated liver, kidney, and brain injury, involving modulation of metalloproteinases and nitric oxide synthase activities in rats.[50,51]

Luteolin shows potential in protecting against environmental pollutant-induced liver damage, such as from phthalates.[52] Specifically, luteolin was identified as a compound that detoxifies di-(2-ethylhexyl) phthalate by facilitating its expulsion from hepatocytes and the liver in mice. The mechanism involves luteolin enhancing degradation of hepatic urocanate hydratase 1 (Uroc1) protein and regulating the urocanic acid/Uroc1 axis.[53] Luteolin also showed efficacy against aflatoxin B1-induced hepatotoxicity in mice and rats, alleviating oxidative stress and apoptosis while activating the Nrf2 signaling pathway.[54,55]

Additionally, luteolin mitigates liver damage induced by lead acetate through antioxidant, anti-inflammatory, and anti-apoptotic activities in rats.[56] Luteolin also demonstrated protective effects against cadmium-induced liver and intestinal toxicity in chickens by regulating the gut-liver axis, alleviating oxidative stress, inflammation, fibrosis, and restoring gut microbiota balance.[57] Against inorganic mercury ($HgCl_2$) exposure, luteolin alleviated liver injury in quails by resisting oxidative stress and promoting mercury ion excretion via the PKCα/Nrf2 pathway.[58] Luteolin attenuated acute $HgCl_2$ hepatotoxicity by regulating the Sirt1/Nrf2/TNF-α signaling pathway in mice and protected against chronic $HgCl_2$ injury via the Nrf2/NF-κB/p53 pathway in rats.[59,60]

In summary, luteolin offers broad-spectrum protection against various hepatotoxins by reducing oxidative stress, inhibiting apoptosis, and modulating inflammatory pathways. Novel delivery systems significantly enhance its solubility and therapeutic efficacy.

Sepsis-induced acute liver injury and transplantation-associated liver injury

The liver is an early target organ in sepsis, and injury may ensue.[61] Luteolin showed protective effects against D-galactosamine (GalN)//LPS-induced fulminant hepatic failure by inhibiting TNF-α–mediated extrinsic and intrinsic apoptotic pathways in mice.[62] Both luteolin and luteolin-7-O-glucoside protected against GalN/LPS-induced hepatotoxicity in ICR mice by regulating inflammatory mediators and antioxidative enzymes, with luteolin being more potent against inflammation and its glucoside more potent in inducing phase II enzymes.[63] Luteolin-7-O-rutinoside from *Pteris cretica* L. var. *nervosa* attenuates LPS/D-gal-induced acute liver injury in mice.[64] A luteolin-phospholipid complex significantly enhanced hepatoprotective potential against GalN/LPS injury in rats.[65] In an LPS-induced acute liver injury mouse model, luteolin ameliorated injury by inhibiting the TXNIP–NLRP3 inflammasome.[66] Additionally, luteolin was found to attenuate hepatic injury in LPS-induced septic mice by regulating P2X7 receptor-based HMGB1 release.[67] In sepsis-induced acute liver injury, luteolin modulated liver macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, thereby exerting protective effects via the TLR4/MyD88/NF-κB signaling pathway, as demonstrated in a sepsis-induced

acute hepatic injury mouse model, mouse bone marrow-derived macrophages, and RAW264.7 cells.[68]

Luteolin also attenuated acute liver allograft rejection in a rat transplantation model by inhibiting T-cell proliferation, regulating T-cell subsets (increasing Tregs and inhibiting Th1 differentiation), and downregulating pro-inflammatory cytokines.[69]

Thus, luteolin mitigates sepsis-induced acute liver injury by inhibiting inflammatory pathways and regulating immune responses, and it attenuates transplant-related liver damage by modulating T-cell activity and cytokine production.

Ischemia-reperfusion (IR) injury

Hepatic IR injury is a common complication of liver surgery and transplantation.[70,71] Luteolin pretreatment attenuated hepatic IR injury in mice by inhibiting inflammation, autophagy, and apoptosis via the extracellular signal-regulated kinase (ERK)/PPARα pathway.[72] An earlier study in rats showed that luteolin preconditioning reduced IR injury by elevating antioxidant capacity (SOD) and HO-1 expression; these effects were blocked by the HO-1 inhibitor zinc protoporphyrin.[73] Therefore, luteolin reduces hepatic IR injury by suppressing inflammation, autophagy, and apoptosis, partly through the ERK/PPARα pathway and enhancement of antioxidant defenses.

Liver fibrosis and cirrhosis

Liver fibrosis is characterized by excessive deposition of extracellular matrix (ECM), primarily by activated hepatic stellate cells (HSCs). Cirrhosis involves severe fibrosis, disruption of liver structure, and loss of liver function.[74,75]

Luteolin exhibits potent anti-fibrotic effects in multiple experimental models. It directly inhibits HSC activation, proliferation, migration, and collagen production. *In vitro*, luteolin suppressed the viability of LX-2 and HSC-T6 cells and reduced the expression of fibrosis markers α-smooth muscle actin, collagen I, and fibronectin via suppression of the STAT3 pathway and by targeting the AKT/mTOR/p70S6K and TGF-β/Smad signaling pathways in rat HSCs and HSC-T6 cells.[76,77] Early studies demonstrated that luteolin inhibits proliferation and collagen synthesis in primary rat HSCs in a dose-dependent manner.[78] It also promoted ECM degradation by increasing matrix metalloproteinase-9 (MMP-9) levels in a CCl_4-induced liver fibrosis mouse model.[79] Luteolin administration attenuated and even reversed fibrosis induced by CCl_4 in rodents,[77,79] as well as in thioacetamide (TAA)-induced liver fibrosis rat models,[80] dimethylnitrosamine-induced models, and bile duct ligation-induced liver fibrosis rat models.[77] A proteomic analysis in HSC-T6 cells revealed that luteolin reversed the expression of several proteins associated with fibrosis progression (e.g., ITIH3, MKI67) and fibrosis protection (e.g., CCR1, CD59) in a TGF-β1-induced HSC-T6 fibrosis model and a CCl_4-induced fibrotic rat model.[81]

The combination of luteolin and silibinin showed synergistic hepatoprotective effects against TAA-induced liver fibrosis in rats.[80] Network pharmacology and transcriptomic analyses led to the development of a novel anti-liver fibrosis formula LLAAF (containing luteolin, licochalcone A, aloe-emodin, and acacetin), which showed synergistic inhibition of HSC proliferation and anti-fibrotic activity in rats via regulation of Jak-STAT and PI3K-Akt-FoxO signaling.[82]

Nanodelivery systems, such as luteolin-loaded exosomes derived from bone marrow mesenchymal stem cells, have been developed and show superior anti-fibrotic effects compared with free luteolin in rats.[83] A dual nanodelivery system combining activated HSC (aHSC)-targeted Ce/Mn bimetallic nanozyme and luteolin-loaded liposomes demonstrated effective targeting of aHSCs, inducing senescence and apoptosis while counteracting oxidative stress, thereby synergistically reversing liver fibrosis, as revealed in HSC-T6 and AML-12 cells and CCl_4-induced liver fibrosis mouse models.[84] Furthermore, luteolin-7-diglucuronide (L7DG), a major flavonoid from *Perilla frutescens* and *Verbena officinalis*, was identified as a potent protein tyrosine phosphatase 1B (PTP1B) inhibitor. L7DG ameliorated HSC activation and liver fibrosis *in vitro* and *in vivo* by inhibiting PTP1B activity and upregulating AMPK phosphorylation in TGF-β1-stimulated mouse primary HSCs, the human HSC line LX-2, and a CCl_4-induced liver fibrosis mouse model.[85] Luteolin also prevents hepatic and adipocyte fibrosis in diet-induced obese mice by targeting the Toll-like receptor (TLR) signaling pathway.[86]

In conclusion, luteolin exerts strong anti-fibrotic effects by inhibiting HSC activation and promoting ECM degradation. Nanoformulations and combination therapies enhance its efficacy in reversing fibrosis.

HCC

HCC is the most common primary liver cancer.[87–91] Luteolin demonstrates multifaceted anti-tumor activities against HCC. It inhibits proliferation, induces cell cycle arrest, and promotes apoptosis in HCC cell lines (e.g., HepG2, SMMC-7721).[92] A combination of transcriptomic and proteomic approaches in HuH-7 cells revealed that luteolin promotes cell cycle arrest and apoptosis through transcription factors such as p53, NF-κB, FOXO, ATF2, and TCF/LEF via targeting AKT1 and SRC and affecting the KEAP1–NRF2 and SRC–STAT3 pathways.[93] Luteolin suppresses HepG2 cell invasion and metastasis by inhibiting hepatocyte growth factor/c-Met, MAPK/ERK, and PI3K-Akt pathways.[94] Recent research elucidated that luteolin suppresses HCC cell migration and invasion by targeting the miR-6809-5p/FLOT1/FAK axis and inhibiting epithelial–mesenchymal transition (EMT) via modulation of the PI3K/AKT/mTOR pathway.[95] Luteolin also inhibits HCC progression promoted by myocyte enhancer factor 2D (MEF2D) through AMOTL2/YAP signaling, as demonstrated in HepG2, Huh7, and PLC/PRF/5 cell models.[96]

Notably, luteolin exerts immunomodulatory effects in H22 tumor-bearing mice by promoting $CD8^+$ T-cell infiltration into tumor tissues and enhancing cytotoxicity, thereby improving anti-tumor immunity and enhancing the efficacy of PD-1 inhibitors.[97] In a DEN-induced mouse liver cancer model, luteolin modulated redox homeostasis and inflammatory cytokines.[98] It also shows synergistic effects with conventional chemotherapeutic agents such as doxorubicin when co-delivered in polymeric micelles.[99] Network pharmacology and transcriptome sequencing studies have identified potential key targets of luteolin in HCC, such as MMP-9 and SRC, and implicated HIF-1α signaling in HepG2 and SMMC-7721 cell models.[92] Luteolin also inhibits arylamine N-acetyltransferase (NAT) activity in human liver tumor cells, which may contribute to its chemopreventive properties.[100] Furthermore, luteolin was identified as a repressor of hepatocyte nuclear factor 4α (HNF4α) in HepG2 cells and mouse models, regulating genes involved in lipid metabolism and ApoB-containing lipoprotein secretion, suggesting mechanisms relevant to both metabolic and anti-tumor effects.[101]

By integrating network pharmacology and bioinformatics, luteolin was validated as a key active compound of *Codonopsis pilosula* (Dangshen) against HCC, inhibiting proliferation and migration while inducing apoptosis and G2/M arrest, potentially via

AKT- or MAPK-JNK–mediated ESR1 signaling.[102] In rat NASH-related hepatocarcinogenesis models, luteolin played a protective role alongside connexin 32, suppressing inflammation, fibrosis, and GST-P-positive foci. Microarray analysis identified brain-expressed X-linked 1 (Bex1) as an upregulated gene, and its knockdown inhibited HCC cell growth.[9]

Recent studies have further elucidated novel mechanisms. Huang *et al*.[103] demonstrated that ginsenoside Rh2 and luteolin synergistically induce cellular senescence to suppress HCC progression. The combination (1:2) inhibited HCC cell proliferation, migration, and invasion, suppressed the Nrf2/HO-1 pathway, and activated the p53/p21 axis, leading to DNA damage-associated senescence; these effects were reversed by the Nrf2 activator sulforaphane. *In vivo*, the combination significantly inhibited tumor growth with good biosafety.[103] Additionally, Li *et al*.[104] showed that luteolin triggers autophagy-dependent ferroptosis in HCC by suppressing SLC40A1-related Fe^{2+} efflux, leading to intracellular Fe^{2+} accumulation, lipid ROS generation, and reduced GSH levels. Inhibition of autophagy reversed these effects, and SLC40A1 overexpression attenuated luteolin-induced ferroptosis, confirming a mechanism involving iron homeostasis and autophagy–ferroptosis crosstalk.[104]

Thus, luteolin exhibits multifaceted anti-tumor activity in HCC. Rather than acting through a single mechanism, it induces apoptosis (via p53 activation and AKT/mTOR inhibition), triggers autophagy-dependent ferroptosis through iron homeostasis disruption, and suppresses metastasis by targeting EMT via the PI3K/AKT/mTOR and miR-6809-5p/FLOT1/FAK axes. This cytotoxicity is complemented by immunomodulatory effects that enhance $CD8^+$ T-cell infiltration and anti-tumor immunity. Synergy with chemotherapy and evidence of senescence induction further highlight its potential in combination therapies.

Viral hepatitis

Chronic hepatitis B virus (HBV) infection is a major risk factor for HCC.[105] Luteolin inhibits HBV replication in HepG2.2.15 cells and in mouse models. The mechanism involves activation of ERK, leading to downregulation of HNF4α, a transcription factor critical for HBV gene expression.[106] Recent research has highlighted the synergistic potential of luteolin with other natural compounds. The combination of Schisandrin C (from *Schisandra chinensis*) and luteolin showed greater inhibition of HBV replication *in vitro* and in an HBV-infected mouse model compared with either compound alone. The mechanism involves luteolin repressing HBV replication via the ERK/HNF4α pathway, while Schisandrin C promotes cGAS–STING pathway activation and IFN-β production in macrophages.[107] Luteolin also affects NAT activity in rat liver,[108] though its direct relevance to viral hepatitis requires further study. Therefore, luteolin inhibits HBV replication by modulating the ERK/HNF4α pathway and shows enhanced antiviral effects when combined with other natural compounds.

Overall, luteolin demonstrates significant therapeutic potential across a wide spectrum of liver diseases, including metabolic, toxic, inflammatory, fibrotic, and malignant conditions. Its mechanisms involve modulation of oxidative stress, inflammation, metabolic pathways, the gut–liver axis, and immune responses (Fig. 1). Advances in drug delivery systems and combination therapies further enhance its efficacy and clinical relevance.

Pharmacological actions and mechanisms of luteolin

The multifaceted hepatoprotective and therapeutic effects of luteolin stem from its ability to modulate several core, interconnected pathophysiological processes. Rather than acting on isolated targets, luteolin often engages a network of pathways that collectively determine cell fate, metabolic flux, and inflammatory tone.

Antioxidant activity

Oxidative stress, driven by an imbalance between ROS production and antioxidant defense, is a universal driver of hepatocyte injury, inflammation, and fibrosis across the spectrum of liver diseases. Luteolin counteracts this not merely as a direct radical scavenger, but as a sophisticated modulator of the cellular defense system (Table 1).[37,47,54,56,58–60,109,110]

The cornerstone of luteolin's antioxidant action is activation of the Nrf2/ARE pathway, the master regulator of the endogenous antioxidant response. In rat primary hepatocytes, luteolin increased protein expression of HO-1 and glutamate-cysteine ligase (GCL) catalytic and modifier subunits, thereby elevating intracellular GSH levels.[109] Interestingly, Nrf2 activation by low-dose luteolin exhibits circadian dependency, being more effective when administered at the start of the active phase in mice.[111] Furthermore, luteolin inhibits ferroptosis by upregulating SLC7A11 and glutathione peroxidase 4 (GPX4) in a CCl_4-induced liver injury mouse model.[37] It also protects against palmitate-induced lipotoxicity in AML12 mouse liver cells and primary mouse hepatocytes by ameliorating ER stress and impaired autophagy, partly through enhanced antioxidant defense.[112] Luteolin (and apigenin) regulate autophagy by targeting NRH-quinone oxidoreductase 2 (NQO2) in HepG2 cells, subsequently affecting AMPK activity.[110] In an inorganic mercury-induced liver injury quail model, luteolin exerted antioxidant effects by promoting mercury ion excretion via the PKCα/Nrf2 pathway.[58]

Additionally, luteolin ameliorated β-cyfluthrin-mediated cytotoxicity in cultured rat primary hepatocytes by attenuating peroxidative and nitrosative stress and augmenting total antioxidant capacity.[113]

Overall, luteolin exerts its antioxidant effects primarily through activation of the Nrf2/ARE pathway, the master regulator of endogenous antioxidant defense, leading to upregulation of key enzymes such as HO-1 and GCL. While the catechol structure of luteolin confers intrinsic radical-scavenging capacity in cell-free systems, the extent to which direct ROS scavenging contributes to its hepatoprotective effects *in vivo* remains to be quantitatively determined, given its low oral bioavailability and extensive metabolism. Luteolin also inhibits ferroptosis through SLC7A11/GPX4 regulation and enhances cellular defense against various toxins, including heavy metals and lipotoxic stress.

Anti-inflammatory activity

Chronic inflammation is a central driver of disease progression from steatosis to steatohepatitis, fibrosis, and HCC. Luteolin targets the inflammatory cascade at multiple hierarchical levels, from extracellular signal reception to downstream effector mechanisms (Table 2).[13–15,50,58,64,66–68,86,106,107]

Luteolin suppresses the production of pro-inflammatory cytokines such as TNF-α, interleukin-1 beta (IL-1β), and IL-18 in a high-carbohydrate diet/HFD-induced NASH rat model and a methotrexate-induced hepatotoxicity rat model.[13,50] Luteolin-7-O-rutinoside protects against LPS/D-gal-induced acute liver injury in mice by inhibiting production of TNF-α, IL-6, and IL-1β and suppressing the PI3K/AKT/AMPK/NF-κB signaling pathway.[64] In a chicken *in vitro* hepatic model, luteolin mitigated *Salmonella Typhimurium* flagellin-induced inflammation by reducing interleu-

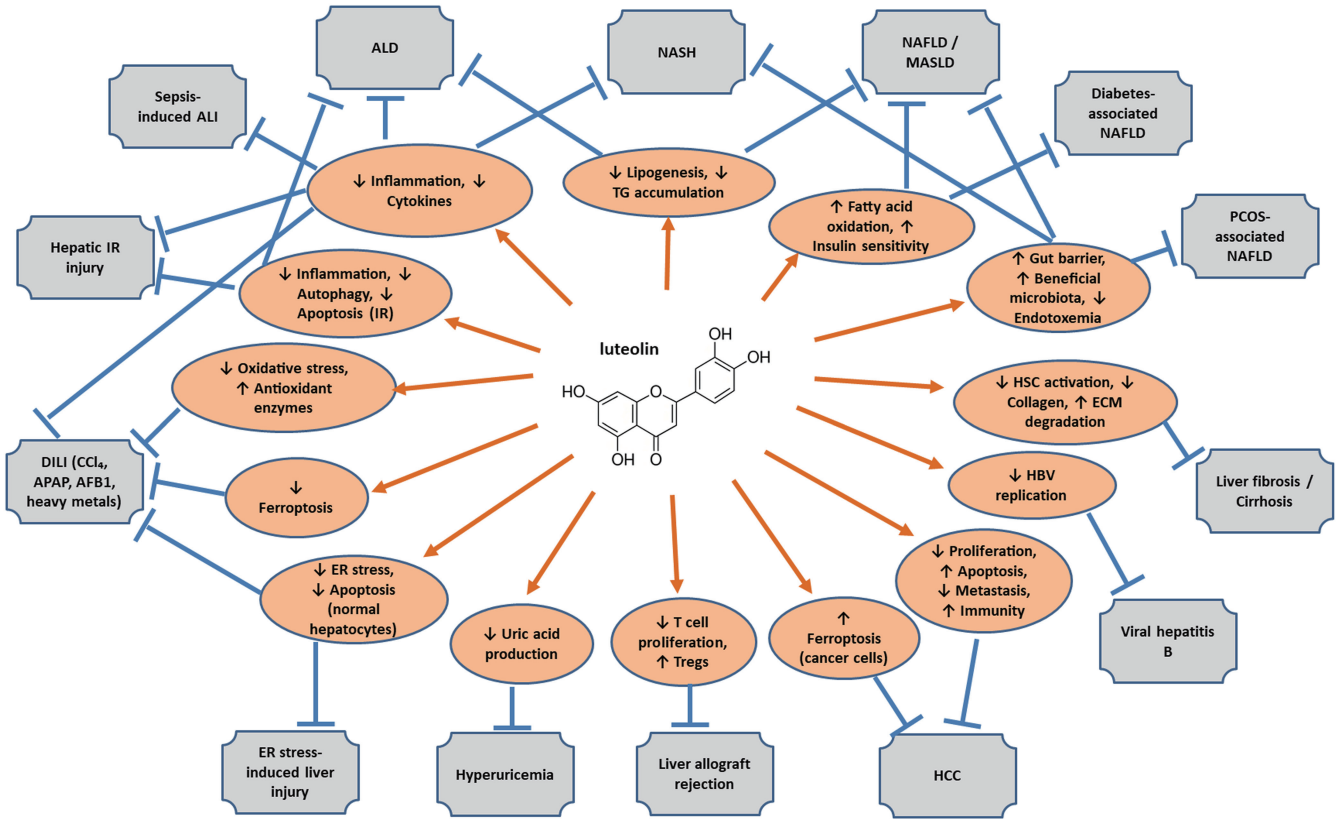

Fig. 1. Luteolin ameliorates liver diseases through multiple pharmacological actions. Orange arrows and ↑: activation, upregulation, or enhancement. T-shaped lines and ↓: suppression, downregulation, or inhibition. AFB1, aflatoxin B1; ALD, alcoholic liver disease; ALI, acute liver injury; APAP, acetaminophen; DILI, drug-induced liver injury; ECM, extracellular matrix; ER, endoplasmic reticulum; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HSC, hepatic stellate cell; IR, ischemia-reperfusion; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PCOS, polycystic ovary syndrome; TG, triglycerides.

kin-8 release and oxidative damage markers.[114] Luteolin inhibits key inflammatory signaling pathways, including NF-κB and TLR cascades, in HFD-induced obese mice and a lead acetate-induced hepatotoxicity rat model.[56,86] It also inhibits expression of iNOS in a pentylentetrazol-induced seizure rat model and a lead acetate-induced hepatotoxicity rat model.[51,56] Additionally, luteolin promotes macrophage polarization toward the anti-inflammatory M2 phenotype, contributing to tissue repair and resolution of inflammation in a bone defect repair rat model and a sepsis-induced acute hepatic injury mouse model.[68,115] This immunomodulatory effect is also leveraged in bone tissue engineering, where luteolin delivery from scaffolds promotes M2 polarization to repair bone

Table 1. Luteolin-targeted molecules and signaling pathways involved in antioxidant and detoxification

Molecule/Pathway connection	Action of luteolin	Consequence of action	References
Nrf2 signaling pathway	Activates the pathway	Promotes the expression of downstream antioxidant enzymes such as HO-1, NQO1, and GCLC	47,54,58,60, 109
PKCα/Nrf2 pathway	Activates the pathway	Promotes the excretion of heavy metals (like mercury)	58
Sirt1/Nrf2/TNF-α pathway	Regulates the pathway	Attenuates oxidative stress and apoptosis induced by toxins like mercuric chloride	56,59
ERK2/Nrf2/ARE pathway	Upregulates via this cascade	Increases antioxidant gene transcription in primary hepatocytes	109
Ferroptosis regulation (SLC7A11 & GPX4)	Regulates SLC7A11 and stimulates GPX4 expression	Inhibits ferroptosis	37
NQO2	Targets the molecule	Regulates autophagy	110

ARE, antioxidant response element; ERK2, extracellular signal-regulated kinase 2; GCLC, glutamate-cysteine ligase catalytic subunit; GPX4, glutathione peroxidase 4; HO-1, heme oxygenase-1; NQO, NAD(P)H quinone oxidoreductase; Nrf2, nuclear factor erythroid 2-related factor 2; PKCα, protein kinase C alpha; Sirt1, sirtuin 1; SLC7A11, solute carrier family 7 member 11; TNF-α, tumor necrosis factor alpha.

Table 2. Luteolin-targeted molecules and signaling pathways involved in anti-inflammation and immunomodulation

Molecule/Pathway connection	Action of luteolin	Consequence of action	References
NF-κB signaling	Suppresses the pathway	Reduces the production of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6	13,50,58,66
TLR4 signaling	Inhibits the pathway	Reduces inflammation in conditions like sepsis and NAFLD	14,15,68,86
TLR4/MyD88/NF-κB mechanism	Inhibits the mechanism	Alleviates sepsis-induced acute hepatic injury	68
P2X7R-RAGE-TLR4 axis	Suppresses the release of HMGB1 through this axis	Attenuates septic liver injury	67
NLRP3 inflammasome (TXNIP-NLRP3)	Inhibits the axis and pathway	Prevents cell death under inflammatory conditions	66
IL-1 and IL-18 pathways	Targets the pathways	Protects against NASH	13,66
cGAS-STING pathway	Promotes activation (combined with Schisandrin C) in hepatitis B context	Induces IFN-β production	106,107

AKT, protein kinase B (PKB); AMPK, AMP-activated protein kinase; cGAS, cyclic GMP-AMP synthase; HMGB1, high-mobility group box 1; IFN-β, interferon beta; IL-18, interleukin-18; IL-1β, interleukin-1 beta; IL-6, interleukin-6; MyD88, myeloid differentiation primary response 88; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor kappa B; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; P2X7R, P2X purinoceptor 7; PI3K, phosphoinositide 3-kinase; RAGE, receptor for advanced glycation end products; STING, stimulator of interferon genes; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor alpha; TXNIP, thioredoxin-interacting protein.

defects.[115]

In summary, luteolin exerts strong anti-inflammatory effects by suppressing key pathways such as NF-κB, TLR4, and NLRP3 inflammasome activation, reducing pro-inflammatory cytokines like TNF-α and IL-1β. It also promotes macrophage polarization toward the anti-inflammatory M2 phenotype, aiding tissue repair and resolution of inflammation.

Anti-fibrotic activity

Liver fibrosis represents a dysregulated wound-healing response, characterized by activation of HSCs into collagen-producing myofibroblasts. Luteolin has a multipronged anti-fibrotic action. It directly targets HSCs, inhibiting their activation, proliferation, migration, and collagen production, and inducing apoptosis via multiple pathways (Table 3),[76,77,85] including TGF-β/Smad, PDGF, STAT3, and AKT/mTOR.[76,77] Early work confirmed its dose-dependent inhibition of primary rat HSC proliferation and collagen synthesis.[78] The novel derivative L7DG exerts anti-fibrotic effects by acting as a potent PTP1B inhibitor, leading to AMPK activation and subsequent HSC inhibition in TGF-β1-activated mouse primary HSCs, the human HSC line LX-2, and CCl_4 alone or in combination with a high-fat/high-carbohydrate diet-induced liver fibrosis mouse model.[85] Crucially, halting fibrosis progression requires not only stopping de novo collagen synthesis but also resolving pre-existing scar tissue. Luteolin also promotes degradation of existing fibrotic tissue by modulating matrix metalloproteinase activity and metallothionein expression in a CCl_4-induced liver fibrosis mouse model.[79]

Thus, luteolin not only directly targets HSCs, inhibiting their activation, proliferation, and collagen production via multiple pathways, but also promotes ECM degradation. This makes luteolin's anti-fibrotic action particularly powerful, as it provides both prevention and reversal of fibrosis.

Anti-steatotic and metabolic modulation

The pathogenesis of NAFLD/MASLD is rooted in an imbalance between lipid acquisition and disposal. Luteolin reprograms hepatic lipid metabolism by simultaneously inhibiting lipogenesis and promoting fatty acid disposal, a dual action that directly addresses the core metabolic lesion through multiple pathways (Table 4).[12,17,18,21,22,26,53,72,101,106,107,116–122]

The suppression of lipogenesis occurs through a concerted mechanism targeting two interconnected transcriptional regulators. Luteolin acts as a direct, competitive inhibitor of LXR, master regulators of lipid metabolism, thereby suppressing the expression of SREBP-1c, the master transcription factor for de novo lipogenesis, in db/db mice and HepG2 cells.[17] This accounts for the reduced expression of lipogenic enzymes, including FASN and ACC, in a chronic-and-binge ethanol feeding mouse model and in RAW 264.7 or HepG2 cells.[26,116] Luteolin also suppresses

Table 3. Luteolin-targeted molecules and signaling pathways involved in anti-hepatic fibrosis

Molecule/Pathway connection	Action of luteolin	Consequence of action	References
TGF-β/Smad signaling	Inhibits the pathway	Suppresses HSC activation	77
STAT3 signaling	Suppresses the pathway	Reduces STAT3 nuclear translocation and transcriptional activity in HSCs	76
AKT/mTOR/p70S6K pathway	Inhibits the pathway	Induces G1 cell cycle arrest and apoptosis in activated HSCs	77
PTP1B	Luteolin-7-diglucuronide acts as an inhibitor	Subsequently upregulates AMPK phosphorylation	85

AKT, protein kinase B (PKB); AMPK, AMP-activated protein kinase; HSC, hepatic stellate cell; mTOR, mammalian target of rapamycin; p70S6K, p70 S6 kinase; PTP1B, protein tyrosine phosphatase 1B; Smad, suppressor of mothers against decapentaplegic; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor beta.

Table 4. Luteolin-targeted molecules and signaling pathways involved in liver metabolic regulation

Molecule/Pathway connection	Action of luteolin	Consequence of action	References
SREBP-1c,-2	Suppresses expression and activation	Inhibits lipogenesis, FAS, cholesterol synthesis	17,18,26,116,117
LXR signaling	Acts as an inhibitor of activation	Downregulates SREBP-1c	17,116
AMPK/PGC-1α pathway	Activates the pathway	Ameliorates hepatic steatosis	118
PI3K/AKT/FoxO1 pathway	Activates the pathway	Ameliorates insulin resistance	12
SIRT1/FoxO1/AMPKα pathway	Inhibits the pathway in visceral adipose tissue	Represses lipolysis	22
AhR	Suppresses AhR activity in hepatocytes	Represses CYP1A1 and GSTP1 expression	119
Nrf2	Suppresses Nrf2 activity in hepatocytes	Represses NQO1 and AKRs expression	119
ERK/PPARα signaling	Activates PPARα and inhibits ERK phosphorylation	Attenuates ischemia-reperfusion injury	72
AdipoR1/AMPK/PPARγ signaling	Modulates the pathway	Relieves metabolic dysfunction-associated fatty liver disease	21
HNF4α	Acts as a repressor	Affects HBV replication and lipid metabolism, which HNF4α is involved in	101,106,107
Uroc1	Targets Uroc1 for degradation	Detoxifies DEHP (phthalates)	53
HTR2B receptor	Binds to the receptor	Inhibits serotonin-induced lipolysis	22
CYP3A subfamily enzymes	Inhibits the enzymes	Affects drug metabolism	121,122
11β-HSD	Increases expression of hepatic 11β-HSD I and renal 11β-HSD II	Enhances the interconversion of active and inactive glucocorticoids	120

11β-HSD, 11β-hydroxysteroid dehydrogenase; AdipoR1, adiponectin receptor 1; AhR, aryl hydrocarbon receptor; AKRs, aldo-keto reductases; AMPK, AMP-activated protein kinase; CYP1A1, cytochrome P450 family 1 subfamily A member 1; CYP3A, cytochrome P450 family 3 subfamily A; DEHP, Di-(2-ethylhexyl) phthalate; D-Gal, D-galactosamine; ERK, extracellular signal-regulated kinase; FAS, fatty acid synthase; FoxO1, forkhead box protein O1; GSTP1, glutathione S-transferase P1; HBV, hepatitis B virus; HNF4α, hepatocyte nuclear factor 4 alpha; HTR2B, 5-hydroxytryptamine receptor 2B; LPS, lipopolysaccharide; LXR, liver X receptor; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinase; PPAR, peroxisome proliferator-activated receptor; SIRT1, sirtuin 1; SREBP, sterol regulatory element-binding protein; Uroc1, urocanate hydratase 1.

SREBP-2 expression and nuclear translocation, thereby modulating cholesterol metabolism in HepG2 cells.[117] Concurrently, luteolin activates AMPK in HFD-induced obese mice and ameliorates hepatic steatosis while enhancing mitochondrial biogenesis via the AMPK/PGC-1α pathway.[10,118] AMPK activation phosphorylates and inactivates ACC, reducing malonyl-CoA levels, and simultaneously relieves inhibition of CPT-1, the rate-limiting enzyme for fatty acid entry into mitochondria for β-oxidation. Luteolin improves insulin sensitivity via the PI3K/AKT/FoxO1 pathway, ameliorating hyperglycemia and insulin resistance associated with NAFLD in HFD and streptozotocin-induced diabetic rat models.[12] Luteolin also lowers uric acid production in hepatocytes, showing potential in managing hyperuricemia in AML12 hepatocytes and ICR mice.[123]

Luteolin acts as a repressor of HNF4α, a nuclear receptor that regulates genes involved in lipid and glucose metabolism, as well as HBV replication, in HepG2 cells and mouse models.[101,106] This repression contributes to its hypolipidemic and anti-HBV effects.

The hepatic metabolic benefits of luteolin also arise from an indirect mechanism that governs inter-organ crosstalk. Luteolin inhibits lipolysis in visceral adipose tissue by antagonizing serotonin signaling via HTR2B in adipocytes, thereby reducing fatty acid flux to the liver in HFD-fed obese mouse models.[22] This effect is independent of its direct actions within hepatocytes.

Luteolin also modulates the expression of drug-metabolizing enzymes (e.g., CYP1A1, NQO1, GSTP1) through the aryl hydrocarbon receptor and Nrf2 pathways in HepG2, Hepa1c1c7, and RL-34 cells.[119] Luteolin significantly increases the gene and protein expression of hepatic 11β-hydroxysteroid dehydrogenase type I (11β-HSD1) and renal 11β-HSD type II (11β-HSD2), enhancing regeneration of active glucocorticoids in the liver and inactivation of glucocorticoids in the kidney, respectively, in rats. This improves glucocorticoid efficacy and reduces adverse drug effects in clinical applications.[120]

Overall, luteolin improves hepatic lipid metabolism by suppressing lipogenesis (via SREBP-1c and LXRs), enhancing fatty acid oxidation (via AMPK/PGC-1α), and reducing fatty acid flux from adipose tissue. It also improves insulin sensitivity through the PI3K/AKT/FoxO1 pathway, regulates drug-metabolizing enzymes, and modulates processes such as uric acid production and glucocorticoid metabolism.

Anti-tumor activity in HCC

Luteolin inhibits angiogenesis, metastasis, and invasion of HCC. It enforces proliferative blockade and cell death through multiple mechanisms (Table 5).[9,93–96,102] Luteolin modulates autophagy in HepG2 cells.[110] It also enhances anti-tumor immunity, particularly by boosting $CD8^+$ T-cell function in an H22 tumor-bearing mouse model,[97] and acts as a repressor of HNF4α, which may contribute to its anti-lipogenic and potential anti-tumor effects in HepG2 cells and mouse models.[101] Recent mechanistic insights include targeting AKT1 and SRC to induce HuH-7 cell death,[93] suppressing the MEF2D/AMOTL2/YAP axis in HepG2, Huh7, and/or SK-Hep1

Table 5. Luteolin-targeted molecules and signaling pathways involved in anti-cancer and cell survival

Molecule/Pathway connection	Action of luteolin	Consequence of action	References
p53 pathway	Activates the pathway	Induces apoptosis and autophagy in cancer cells	103,124
AKT1 and SRC	Identifies them as direct targets	Inhibits liver cancer cell proliferation	93
AMOTL2/YAP signaling	Inhibits the pathway	Suppresses hepatocellular carcinoma progression	96
miR-6809-5p/FLOT1/FAK axis	Targets this axis	Suppresses cell migration and invasion	95
PI3K/AKT/mTOR pathway	Modulates the pathway	Suppresses EMT	95
HGF/c-Met (involving MAPK/ERKs and PI3K-Akt)	Suppresses the phosphorylation of c-Met	Inhibits HGF-induced invasion involving these pathways	94
ESR1 (via AKT or MAPK-JNK signaling)	Modulates ESR1 via these signals	Exerts anti-HCC effects	102
Connexin 32/ Bex1 pathway	Luteolin and Connexin 32 co-inhibits the Bex1 expression	Inhibits HCC cell growth	9

AKT, protein kinase B (PKB); AKT1, AKT serine/threonine kinase 1; AMOTL2, angiomotin-like protein 2; Bex1, brain-expressed X-linked 1; c-Met, mesenchymal-epithelial transition factor; EMT, epithelial-mesenchymal transition; ERKs, extracellular signal-regulated kinases; ESR1, estrogen receptor 1; FAK, focal adhesion kinase; FLOT1, flotillin-1; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; p53, tumor protein p53; PI3K, phosphoinositide 3-kinase; SRC, proto-oncogene tyrosine-protein kinase Src; YAP, Yes-associated protein.

HCC cell lines,[96] and inhibiting migration and invasion via the miR-6809-5p/FLOT1/FAK pathway and EMT in MHCC97-H and HuH-7 cells.[95] Luteolin and connexin 32 co-inhibit Bex1 expression, resulting in inhibition of HCC cell growth in a rat NASH-related hepatocarcinogenesis model.[9] Luteolin inhibits HCC cell growth through activating P53 way.[103,124] Therefore, luteolin is a multi-modal agent capable of suppressing HCC by inducing apoptosis, causing cell cycle arrest, inhibiting metastasis, and activating immune responses through multiple pathways.

Anti-apoptotic and pro-survival effects in injured hepatocytes

Luteolin regulates hepatocyte cell fate in a context-dependent manner. In contrast to its pro-apoptotic role in cancer cells, luteolin protects normal hepatocytes from apoptosis under stress. It modulates the Bcl-2 family balance (increasing the Bcl-2/Bax ratio), inhibits caspase activation, and ameliorates ER stress in models of GalN/LPS-induced fulminant hepatic failure in mice, APAP-induced L02 cell injury, tunicamycin-induced ER stress, and palmitate-induced hepatic lipotoxicity.[40,47,62,112] In METH-induced rat hepatotoxicity, luteolin alleviates apoptosis by suppressing the p53 pathway.[49] By reducing ER stress and restoring autophagic flux, luteolin promotes survival of AML12 mouse liver cells and primary mouse hepatocytes treated with palmitic acid.[112] It also protects against doxorubicin-induced hepatorenal toxicity in rats by reducing oxidative and inflammatory stress and suppressing apoptosis.[125] Therefore, in non-cancerous liver cells, luteolin protects against apoptosis by modulating Bcl-2 family proteins, inhibiting caspases, and alleviating ER stress. It promotes hepatocyte survival under toxic, metabolic, or drug-induced stress, highlighting its cytoprotective role in liver injury. This selective pro-survival behavior—inducing death in malignant cells while protecting nonmalignant hepatocytes—makes luteolin a promising therapeutic candidate. However, the underlying mechanisms by which luteolin discriminates between these two cellular contexts within the same liver remain to be elucidated, representing a critical knowledge gap for its translational development.

Regulation of the gut–liver axis

Luteolin targets the gut–liver axis at two levels to break the cycle of inflammation-driven liver injury. It helps restore gut microbiota diversity (e.g., increasing *Bacteroidota* and decreasing *Firmicutes*) and intestinal barrier function, thereby reducing endotoxemia and subsequent hepatic inflammation in HFD-fed rats, an MCDD-induced NASH mouse model, and an obese polycystic ovary syndrome rat model.[11,14–16] Luteolin restores gut microbiota balance, improves intestinal barrier integrity, and reduces endotoxemia, thereby mitigating liver inflammation and injury. This mechanism is particularly important in NAFLD and toxin-induced liver injury models, emphasizing the role of the gut–liver axis in its therapeutic effects.

Overall, luteolin exhibits a broad and multifaceted pharmacological profile against liver diseases, primarily through its potent antioxidant, anti-inflammatory, anti-fibrotic, anti-steatotic, and anti-tumor activities. Its mechanisms involve modulation of key signaling pathways (e.g., Nrf2, NF-κB, AMPK, and TGF-β), regulation of the gut–liver axis, and selective pro-survival effects in healthy hepatocytes (Fig. 2). These diverse actions underscore its therapeutic potential across metabolic, inflammatory, fibrotic, and malignant liver conditions.

Pharmacokinetics of luteolin

Luteolin undergoes extensive pre-systemic metabolism (glucuronidation and sulfation, primarily in the liver and intestine) after oral administration. It undergoes rapid phase I and II metabolism, producing metabolites such as apigenin, chrysoeriol, diosmetin, and various conjugates in rat liver and cultured hepatocytes.[123,126–129] While some metabolites may retain activity, they are also quickly eliminated. Studies using primary cultured rat hepatocytes showed extensive first-pass metabolism of luteolin and apigenin, with elimination exceeding 90% after 120 min. Metabolism and drug–drug interactions in primary cultured rat hepatocytes can be influenced by other flavonoids present in extracts.[127] Luteolin and diosmetin have been shown to inhibit CYP3A4/3A5 activity *in vitro*, potentially causing pharmacokinetic interactions.[121] Interestingly, luteolin itself can induce the formation of a reactive ortho-benzoquinone metabolite via CYP3A-mediated metabolism, contributing to cytotoxicity in primary rat hepatocytes by depleting GSH.[122]

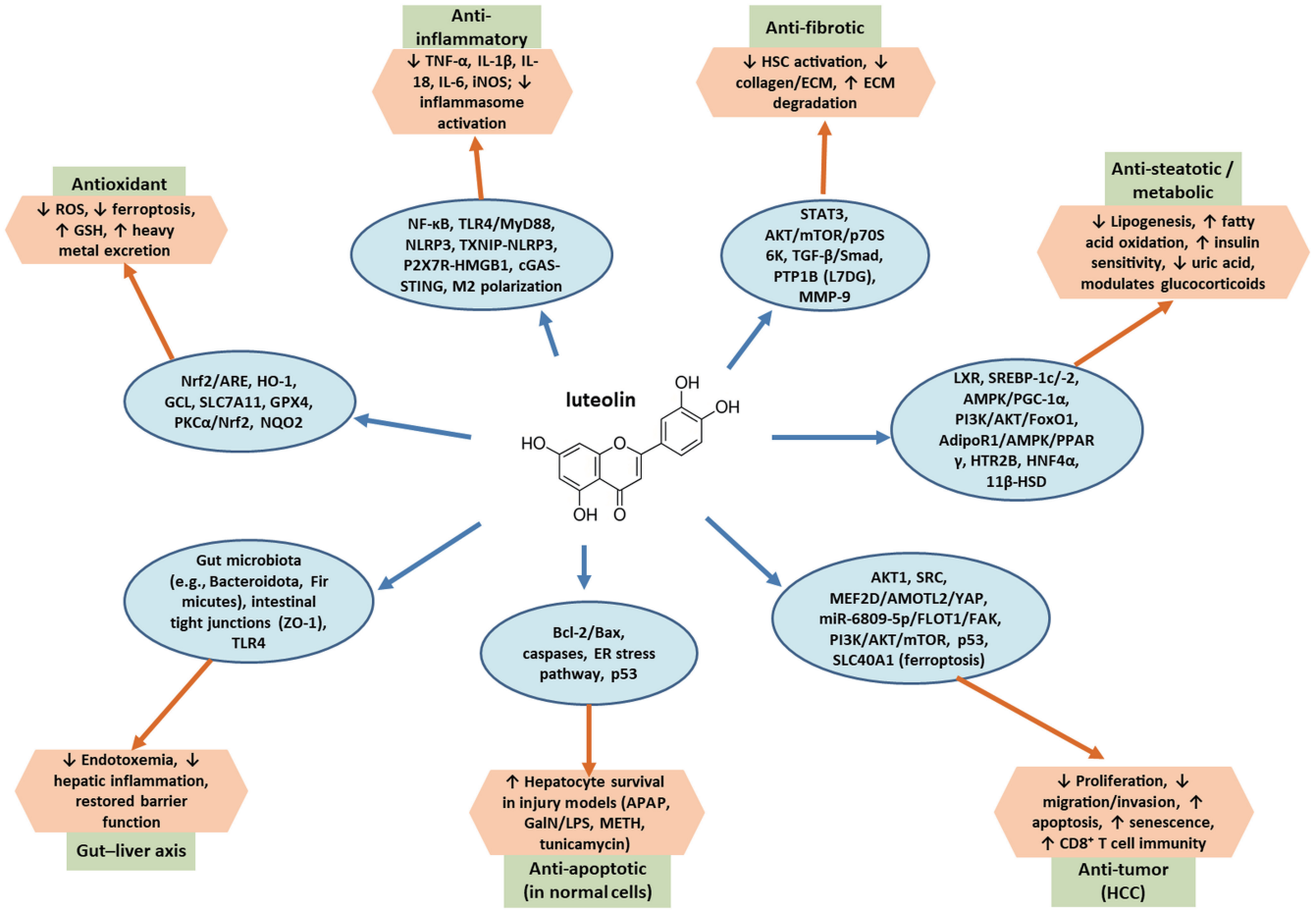

Fig. 2. Molecular targets and pathways mediating pharmacological actions of luteolin. Blue arrows, orange arrows and ↑: activation, upregulation, or enhancement. ↓: suppression, downregulation, or inhibition. 11β-HSD, 11β-hydroxysteroid dehydrogenase; AdipoR1, adiponectin receptor 1; AKT, protein kinase B (PKB); AMOTL2, angiomotin-like protein 2; AMPK, AMP-activated protein kinase; APAP, acetaminophen; ARE, antioxidant response element; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; cGAS, cyclic GMP-AMP synthase; ECM, extracellular matrix; ER, endoplasmic reticulum; FAK, focal adhesion kinase; FLOT1, flotillin-1; FoxO1, forkhead box protein O1; GalN, D-galactosamine; GCL, glutamate-cysteine ligase; GPX4, glutathione peroxidase 4; GSH, glutathione; HCC, hepatocellular carcinoma; HMGB1, high mobility group box 1; HNF4α, hepatocyte nuclear factor 4 alpha; HO-1, heme oxygenase 1; HSC, hepatic stellate cell; HTR2B, 5-hydroxytryptamine receptor 2B; IL, interleukin; iNOS, inducible nitric oxide synthase; L7DG, luteolin-7-diglucuronide; LPS, lipopolysaccharide; LXR, liver X receptor; MEF2D, myocyte enhancer factor 2D; METH, methamphetamine; miR, microRNA; MMP-9, matrix metallopeptidase 9; mTOR, mammalian target of rapamycin; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor-kappa B; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NQO, NAD(P)H quinone oxidoreductase; Nrf2, nuclear factor erythroid 2–related factor 2; P2X7R, P2X purinoceptor 7; p53, tumor protein p53; p70S6K, p70 S6 kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinase; PKCα, protein kinase C alpha; PPARγ, peroxisome proliferator-activated receptor gamma; PTP1B, protein tyrosine phosphatase 1B; ROS, reactive oxygen species; SLC40A1, solute carrier family 40 member 1; SLC7A11, solute carrier family 7 member 11; Smad, suppressor of mothers against decapentaplegic; SRC, Src; SREBP, sterol regulatory element-binding protein; STAT3, signal transducer and activator of transcription 3; STING, stimulator of interferon genes; TGF-β, transforming growth factor beta; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor alpha; TXNIP, thioredoxin-interacting protein; YAP, Yes-associated protein; ZO-1, zonula occludens-1.

Liver uptake of luteolin and its glucuronides (L-3′-G and L-7-G) is primarily mediated by organic anion transporting polypeptides OATP1B1 and OATP1B3, which show selective uptake of L-3′-G in a study using OATP-overexpressing cell systems.[130] Due to poor aqueous solubility, extensive pre-systemic metabolism, and rapid systemic clearance, the oral bioavailability of luteolin is very low.

Distribution of luteolin in the liver is modulated by liver hemodynamics, which may be affected by liver diseases. The liver is the only organ in the body that receives a dual blood supply, with the portal vein contributing approximately 75% of blood flow and the hepatic artery contributing approximately 25%. Orally administered luteolin is absorbed in the intestine and enters the liver via the portal vein. Therefore, the initial concentration of luteolin in its parent form is highest in the periportal zone, which is beneficial for its pharmacological effects. In contrast, the perivenous zone is located around the terminal hepatic venules; by the time the drug reaches this area, most of it has already been metabolized, resulting in very low concentrations of the parent drug, which is unfavorable for pharmacological action. Diseases such as liver cirrhosis can reduce portal blood flow, with compensatory dilation of the hepatic artery, thereby altering the intrahepatic concentration of luteolin.

Liver diseases also affect the metabolism of luteolin. Under inflammatory conditions, the expression of CYP3A4 is reduced through interaction between NF-κB and the retinoid X receptor.[131]

In addition, hepatic mRNA expression of *Ugt1a1*, *Ugt1a9*, and *Ugt2b5* is reduced in mice, while *UGT1A4*, *UGT2B4*, and *UGT2B7* are reduced in human livers.[132,133] There is significant interindividual variation in the levels of various isoforms of UGTs.[133]

Therefore, it is necessary to study the local pharmacokinetics of luteolin in various liver diseases to identify dosing strategies that ensure target luteolin concentrations in the liver and achieve therapeutic efficacy.

Limitations

This review provides a comprehensive overview of the therapeutic applications and pharmacological actions of luteolin in liver diseases; however, several limitations should be considered when interpreting the evidence. (1) The review is purely descriptive and lacks a critical appraisal of the methodological quality or risk of bias in the included preclinical studies, as well as any quantitative synthesis (e.g., meta-analysis) to determine the overall effect size of luteolin across different disease models or mechanisms. (2) The scope encompasses an extraordinarily wide range of liver conditions (NAFLD/MASLD, ALD, DILI, sepsis-induced injury, IR injury, fibrosis, HCC, and viral hepatitis) and heterogeneous experimental models (different animal species, disease induction methods, dosing regimens, and endpoints). While this breadth demonstrates the broad activity of luteolin, the extreme heterogeneity limits the ability to make direct comparisons or draw strong, specific mechanistic conclusions, and the review does not systematically address this heterogeneity. (3) All mechanistic depth and most efficacy evidence are drawn from animal and *in vitro* models. Although human pharmacokinetic data and one randomized controlled trial on a luteolin-containing combination supplement (Altilix®) are cited, isolated luteolin has not been rigorously tested in human liver disease populations. The entire review therefore largely represents a synthesis of potential rather than proven human effects. (4) The pharmacokinetic limitations of luteolin, including poor aqueous solubility, extensive first-pass metabolism, low oral bioavailability, and complex liver distribution and metabolism under various disease conditions, are acknowledged, and many cited studies employ advanced nanodelivery systems to overcome these barriers. However, the patterns of hepatic distribution and metabolism under different liver disease states remain to be fully delineated, and the long-term safety and toxicology of these novel formulations remain underexplored; furthermore, the translational relevance of these delivery strategies to clinical practice is still uncertain. (5) Finally, while the review discusses numerous signaling pathways and molecular targets (summarized in Tables 1–5), the interconnected and sometimes contradictory nature of luteolin's actions (e.g., pro-apoptotic in HCC cells versus anti-apoptotic in normal hepatocytes) is not critically analyzed, and the relative contribution of luteolin metabolites to its overall pharmacological effects remains to be fully elucidated. In summary, while luteolin exhibits promising hepatoprotective and therapeutic potential across a broad spectrum of liver diseases in preclinical settings, its translation into clinical practice requires rigorous human studies, standardized experimental frameworks, and thorough safety evaluations of advanced delivery systems before definitive conclusions can be drawn regarding its efficacy in human liver disease populations.

Future research perspectives

Luteolin is a multifaceted natural compound with immense therapeutic potential against a wide spectrum of liver diseases. Its hepatoprotective and anti-hepatocarcinogenic effects are mediated through a complex and interconnected network of signaling pathways targeting oxidative stress, inflammation, metabolic dysfunction, fibrogenesis, and tumor progression. The breadth of evidence from *in vitro* and *in vivo* studies is compelling. To translate these findings into clinical reality, several key areas should be the focus of future research.

Rigorous human clinical trials

While numerous animal studies and one human trial on a combination supplement exist,[20] well-designed, randomized, double-blind, placebo-controlled clinical trials are imperative to definitively establish the efficacy, optimal dosing, and safety profile of luteolin (and its optimized formulations) in humans with specific liver conditions (e.g., NASH, early fibrosis, or as an adjuvant in HCC). The promising results from advanced delivery systems in preclinical studies warrant translation into clinical trials.

Exploration of synergistic combinations

Luteolin has pleiotropic mechanisms, making it an ideal candidate for combination therapy. Research should explore its synergy with existing standard-of-care drugs (e.g., metformin for NAFLD, sorafenib for HCC, antivirals for hepatitis) or other nutraceuticals. Promising preclinical examples include luteolin with silibinin for fibrosis,[80] with gallic acid for ALD,[28] with metformin for chemical injury,[39] and with Schisandrin C for HBV.[107] Rational combination formulations such as LLAAF also hold promise.[82]

Elucidation of metabolite activity and the gut–liver axis

Further studies are needed to delineate the contribution of luteolin metabolites to its overall effects. The discovery of L7DG as a potent PTP1B inhibitor underscores that metabolites may possess unique and potent bioactivities.[85] Additionally, modulation of the gut microbiota and the gut–liver axis by luteolin represents a promising area linking its local hepatic actions with systemic metabolic health, warranting deeper investigation.[11,14–16,43,57]

Development of cell-type-specific delivery systems

Despite its promising pharmacological profile, the clinical translation of luteolin is significantly hampered by unfavorable pharmacokinetic properties. Future formulation strategies should aim to improve bioavailability and achieve greater specificity, including delivery systems that actively target specific liver cell types (e.g., aHSCs for fibrosis, Kupffer cells for inflammation, hepatocytes for steatosis, or cancer cells for HCC) using ligand–receptor interactions, as exemplified by aHSC–targeted dual systems or nanotechnology-enabled delivery.[84,134]

Long-term safety and toxicology studies

Comprehensive chronic toxicity studies of novel luteolin formulations are necessary to ensure safety for potential long-term use in managing chronic liver diseases. While luteolin generally has a favorable safety profile, studies noting CYP3A-mediated formation of a reactive metabolite and GSH depletion in primary hepatocytes at certain concentrations highlight the need for careful dose and formulation optimization.[122]

In summary, luteolin demonstrates significant hepatoprotective and anti-hepatocarcinogenic potential in preclinical models of liver disease. However, clinical translation requires rigorous human trials, exploration of synergistic combinations, elucidation of gut–liver axis mechanisms, development of cell-type-specific delivery

systems, and comprehensive long-term safety evaluation. Addressing these challenges will be essential to transform this multifaceted natural compound into an effective therapy for chronic liver conditions.

Conclusions

Compelling preclinical evidence supports luteolin as an agent with multi-target therapeutic potential across a broad spectrum of hepatic disorders. Its pharmacological efficacy is mediated through the modulation of critical signaling pathways such as Nrf2, NF-κB, AMPK, TGF-β, and the gut–liver axis. Luteolin demonstrates robust hepatoprotective effects by mitigating oxidative stress, inflammation, and metabolic dysfunction in models of NAFLD/MASLD and ALD. Furthermore, it offers broad-spectrum protection against drug- and toxin-induced injury, sepsis-related damage, and IR injury. Notably, luteolin acts as a potent antifibrotic agent by inhibiting HSC activation and exhibits anti-HCC activity by inducing cell cycle arrest, apoptosis, senescence, and ferroptosis, while concurrently enhancing antitumor immunity. To translate these findings into clinical application, it is critical to develop advanced delivery systems to overcome its limited bioavailability, explore synergistic combinations, and conduct rigorous human trials, thereby transforming luteolin from a dietary phytochemical into a validated therapeutic agent.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study conception, writing of the manuscript (WL, XG), and study supervision (XG). Both authors have approved the final version and publication of the manuscript.

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