Research progress on the protective effect and oxidative stress mechanism of rutin against liver injury (Review)

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Abstract. Addressing the global health burden of liver injury necessitates the exploration of novel prevention and treatment strategies. The therapeutic use of the natural flavonoid rutin, which is renowned for its notable antioxidant properties, has emerged as a promising area of research. The present review systematically examines the protective mechanisms of rutin and research progress on its use across various liver-injury models. Primarily, the present review assesses the current knowledge and therapeutic challenges of liver injury, emphasizing the requirement for in-depth studies on its pathogenesis and the development of innovative treatment approaches. Given the widespread recognition of oxidative stress as a key contributor to liver injury, the present review specifically details the effects of oxidative stress on biological macromolecules, as well as the central roles of the nuclear factor erythroid 2-related factor 2 and nuclear factor-κB pathways in modulating antioxidant, anti-inflammatory and apoptotic responses. Building on this foundation, the present review critically evaluates the antioxidant properties of rutin and its hepatoprotective effects, which are mediated through regulation of the aforementioned pathways. Furthermore, the potential of nanotechnology to enhance the bioavailability and delivery efficiency of rutin is explored. By synthesizing mechanistic evidence and evaluating nano-strategies, the present review establishes a coherent framework for the hepatoprotective activities of rutin, thereby advancing the field towards mechanism-guided therapeutic development and targeted delivery solutions for liver injury.

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Contents

1. Introduction

Liver diseases represent a notable global health challenge, affecting hundreds of millions of individuals globally (1,2). Recent data indicate that cirrhosis and other chronic liver conditions have become the 10th leading cause of death globally, resulting in ~2 million deaths annually. These conditions account for 4% of total global mortality and rank as the 15th leading contributor to disability-adjusted life years (3,4). In addition to the human toll, liver diseases place a notable strain on the global economy, with medical costs for patients with chronic liver disease exceeding $32 billion in 2016 alone (5). The core pathological process underlying these diseases is liver injury, a condition characterized by the structural and functional impairment of the liver resulting from various internal and external factors. Oxidative stress has been recognized as a key pathogenic factor in liver injury and the excessive generation of reactive oxygen species (ROS) is closely linked to the progression of liver diseases, as reviewed by Rezzani and Franco (6). Currently, the clinical management of liver injury focuses on removing causative factors, alleviating symptoms, modulating immune responses and providing supportive care. However, existing therapies for liver injury fall short in precisely targeting and regulating the oxidative-inflammatory cascade (7-9). Thus, the development of novel strategies aimed at modulating key oxidative signaling pathways remains an important challenge for liver injury prevention and treatment.

Natural flavonoids have previously garnered attention as promising candidates for therapeutics in liver injury prevention and treatment, owing to their multi-target regulatory properties (10). Rutin, a naturally occurring flavonol, consists of quercetin linked to a rutinose molecule via a glycosidic bond

at the C-3 position (11,12). Rutin is found in various plants, such as buckwheat, citrus fruits, quinoa and sophora root (13), and demonstrates a wide array of biological effects, including the prevention of platelet aggregation, hormonal regulation, inhibition of adipogenesis, and anti-inflammatory and antioxidant activities (14-17). These effects have been shown to contribute to alleviating liver injury caused by various etiologies (18-20). In non-alcoholic fatty liver disease (NAFLD), rutin has been shown to markedly inhibit lipid synthesis, enhance fatty acid metabolism, reduce lipid accumulation in hepatocytes and decrease oxidative damage, ultimately improving liver pathology and function (21).

Rutin is primarily utilized in clinical settings for the treatment of conditions associated with increased capillary fragility, such as chronic venous insufficiency and hemorrhoids, with evidence showing that flavonoid mixtures containing rutin can safely and effectively manage hemorrhoidal bleeding (22). Rutin also serves as an adjuvant therapy for hypertension and diabetic microangiopathy. In patients with type 2 diabetes, rutin supplementation has been shown to markedly reduce glycosylated hemoglobin, lipid and fasting blood glucose levels, while improving the total antioxidant capacity of patients (23). The mechanism of action of rutin involves the enhancement of vascular endothelial function and the alleviation of oxidative damage (24). A 5-year prospective registry study further corroborated that hydroxyethyl rutin (HR) demonstrated a notable therapeutic effect on edema and capillary filtration rate in patients with venous hypertension and diabetic microangiopathy. Treatment with higher HR doses (2 g/day in diabetic patients) produced greater reductions in swelling than lower doses and resulted in notable improvements in clinical symptom scores; HR also played a protective role against the formation of venous ulcers. Additionally, HR treatment was associated with a notable decrease in total cholesterol levels in patients, and no adverse effects or intolerances were observed. Notably, the high levels compliance (>85%) were observed over the 5-year period (25). Currently, there remains a lack of high-quality clinical trials specifically evaluating the hepatoprotective effects of rutin in patients with liver injury. The majority of available evidence supporting these effects has been derived from preclinical animal models and *in vitro* studies, therefore high-quality randomized controlled trials are required to support the efficacy and safety of rutin administration in humans (26,27). As such, rutin has previously demonstrated notable promise as a broad-spectrum hepatoprotective agent, but its clinical translation requires further investigation.

Research on the preventive and therapeutic effects of rutin in various liver-injury models, as well as its mechanisms of action in oxidative stress modulation, has been increasing. The hepatoprotective effects of rutin involve multiple mechanisms, including antioxidant, anti-inflammatory and anti-apoptotic activities, with oxidative stress serving as the central link (28). The present review aims to systematically summarize research on the effects of rutin in chemical, drug-induced, alcohol-induced and other liver-injury models, with a focus on the role of rutin in oxidative stress. Additionally, the present review explores emerging strategies for nano-targeted drug delivery based on the antioxidant effects of rutin. By synthesizing these studies, the present review provides theoretical support for the clinical application of rutin as a novel approach to treating or preventing liver injury.

The data sources for the present study were searched in PubMed (https://pubmed.ncbi.nlm.nih.gov/), using a combination of medical subject heading terms and free-text terms. The key words included 'rutin', 'liver injury', 'oxidative stress', 'Nrf2', 'NF-κB' and 'nanodelivery'. All included literature consisted of original research or reviews published in peer-reviewed journals.

2. Role of oxidative stress in the development and progression of liver injury

The onset and progression of liver disease are pathologically linked to oxidative stress-induced injury. Oxidative stress originates from an imbalance between intracellular antioxidant defenses and ROS, which disrupts cellular redox states and causes oxidative damage. As byproducts of oxidative metabolism, ROS are generated through both endogenous pathways, such as electron leakage from the mitochondrial electron transport chain, cytochrome P450 enzyme metabolism in the endoplasmic reticulum and respiratory bursts in immune cells, particularly Kupffer cells in the liver, as well as exogenous factors, for example alcohol, drugs and environmental toxins (28,29). Chronic overproduction of ROS directly activates the oxidative stress system, causing irreversible modifications to various biomacromolecules via lipid peroxidation, protein carbonylation, DNA oxidative damage and protein misfolding; as such, activation of the oxidative-stress system also results in altered cellular metabolism, tissue remodeling mediated by misfolded proteins and genomic instability (30,31). Concurrently, oxidative stress disrupts complex intracellular signaling pathways, triggering a cascade of reactions that escalate from molecular damage to signaling dysregulation. This cascade has been shown to amplify oxidative injury, activate inflammatory responses and apoptotic pathways and drive the pathological progression of liver disease (32), as summarized in Fig. 1, with additional mechanistic details presented in the figure. Hence, oxidative stress serves as a central axis linking initial hepatic injury to subsequent disease progression.

Recent research has highlighted the notable roles of biological processes, such as oxidative stress, inflammation and apoptosis, in the defense against liver injury (33). Consequently, understanding the specific mechanisms underlying the oxidative-stress, inflammatory and apoptotic signaling pathways in liver injury progression is important for developing novel strategies to prevent and treat liver diseases.

Nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway-mediated oxidative stress response and liver protection mechanisms. Nrf2 is the central regulator of the cellular antioxidant defense system, and its activation has demonstrated protective effects in various liver diseases and hepatotoxicity models (34,35). In physiological conditions, Nrf2 is sequestered by kelch-like ECH-associated protein 1 (Keap1) and subsequently targeted for ubiquitin-dependent degradation, which maintains a low basal activity. Oxidative stress or electrophiles trigger the dissociation of Nrf2 from Keap1, resulting in the nuclear translocation

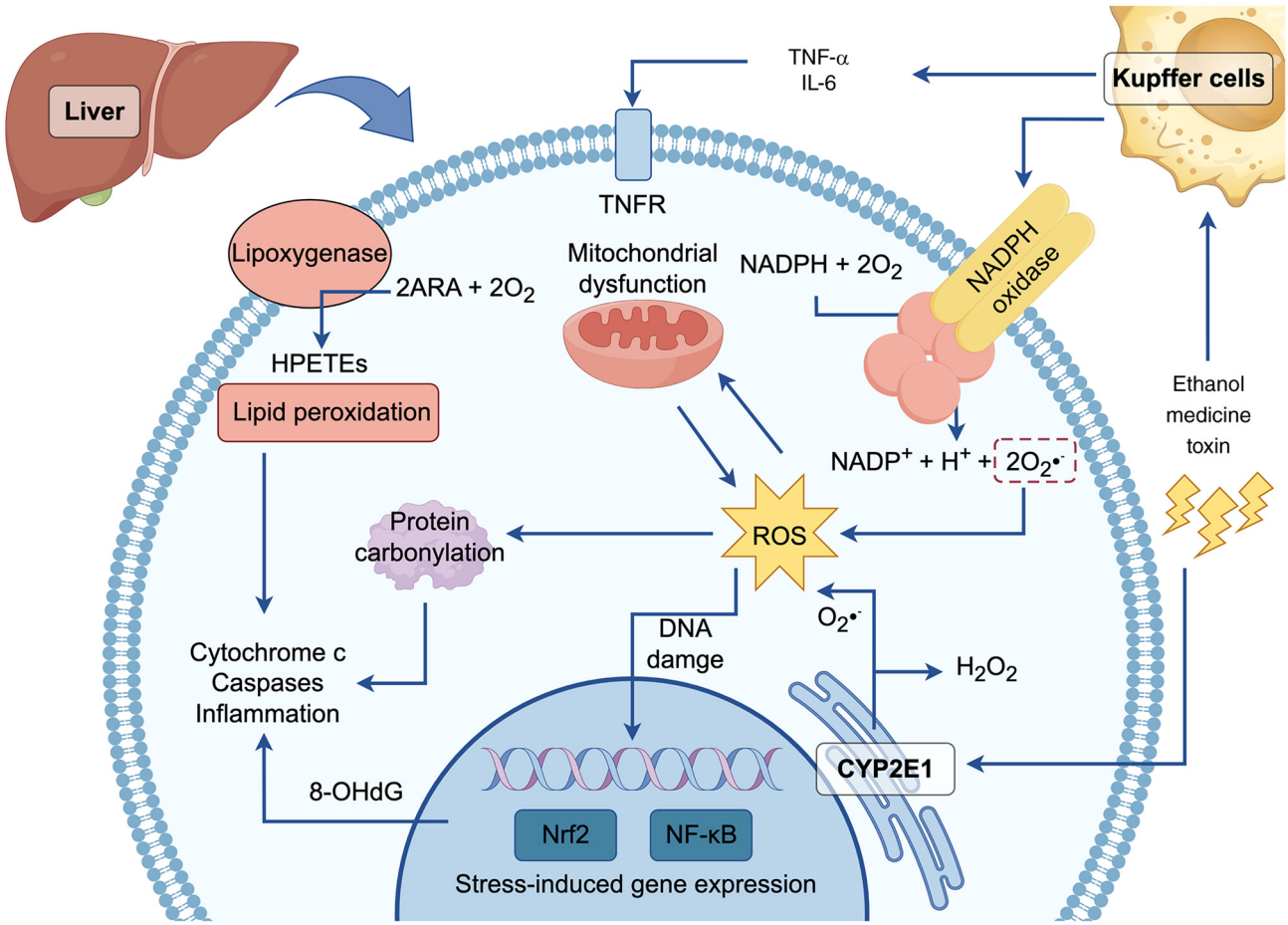

Figure 1. Pathological mechanism of oxidative stress-mediated liver injury. Oxidative stress triggers excessive ROS production from both endogenous and exogenous sources, leading to biomacromolecular damage and a dysregulated signaling cascade, which collectively perpetuates the pathogenesis of liver disease. 8-OHdG, 8-hydroxy-2'-deoxyguanosine; ARA, arachidonic acid; CYP2E1, cytochrome P450 2E1; HPETEs, hydroperoxyeicosatetraenoic acids; IL-6, interleukin-6; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; TNFR, tumor necrosis factor receptor.

of Nrf2 and its binding to ARE elements, which in turn drives the transcription of antioxidant target genes (35-38). These genes work synergistically to maintain intracellular redox balance (39). Under certain conditions, the upregulation of HMG-CoA reductase degradation protein 1 promotes the degradation of Nrf2, forming a negative feedback loop that prevents excessive activation of this pathway (40) (Fig. 2).

Notably, sustained or excessive activation of Nrf2 may confer potential pathological risks under specific pathological liver conditions. In hepatocellular carcinoma (HCC), aberrant activation of Nrf2 has been shown to drive tumor progression and potentiate invasion and metastasis (35,36). Additionally, Nrf2 activation has been shown to mediate immune escape and compromise the tumoricidal capacity of immune cells (41,42). Furthermore, Nrf2 signaling upregulates a spectrum of genes responsible for drug efflux and cellular detoxification, which reduces the intracellular accumulation of chemotherapeutic agents and neutralizes their cytotoxic effects, ultimately inducing tumor chemoresistance (43). Summarily, transient Nrf2 activation protects against hepatic oxidative damage, but sustained dysregulation of this signaling pathway disrupts hepatic homeostasis and accelerates malignant transformation in chronic liver disease and premalignant lesions (44,45). Thus, the Nrf2/ARE pathway represents a core antioxidant system and an important target for liver disease intervention.

Several animal models of liver diseases have supported the notable antioxidative role of the Nrf2/ARE pathway. Jujuboside A has been shown to mitigate oxidative damage, mitochondrial dysfunction and apoptosis caused by hepatic ischemia-reperfusion (I/R) by activating the Akt/Nrf2/ARE pathway and subsequently upregulating heme oxygenase 1 (HO-1) expression via ARE-driven transcription, promoting Nrf2 nuclear translocation and increasing HO-1 expression (46). Similarly, bilirubin has been shown to trigger antioxidant mechanisms through activation of the Nrf2/ARE pathway and induction of HO-1 expression, demonstrating potential for clinical applications (35). In conclusion, the Nrf2/ARE pathway plays an important role in mediating oxidative stress and cytoprotection by maintaining redox homeostasis, thus alleviating liver injury. Experimental evidence has supported the therapeutic potential of treatments modulating the Nrf2 signaling pathway in various types of liver injury, highlighting its promise as a molecular target for liver disease prevention and treatment (47).

Regulatory role of the nuclear factor-κB (NF-κB) pathway in oxidative stress-induced hepatic inflammation. During the oxidative stress-driven hepatic inflammatory process,

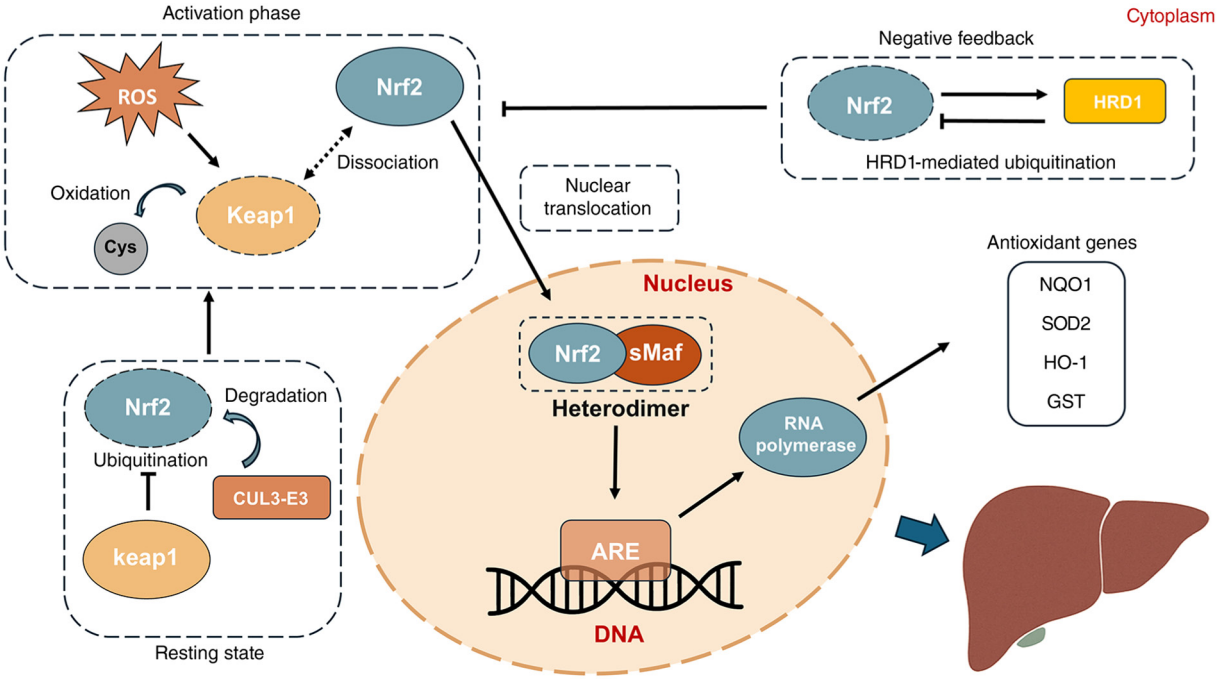

Figure 2. Antioxidant regulatory mechanism of the liver Nrf2 signaling pathway. Under basal conditions, Nrf2 is bound by Keap1 and targeted for degradation. In conditions of oxidative stress, Nrf2 dissociates, translocates to the nucleus and binds to the ARE to transactivate genes, such as SOD2 and HO-1, thereby restoring redox homeostasis. The Nrf2 pathway is tightly regulated by a negative feedback loop involving HRD1-mediated degradation of Nrf2. ARE, antioxidant response element; CUL3, cullin 3; Cys, cysteine; GST, glutathione S-transferase; HO-1, heme oxygenase 1; HRD1, HMG-CoA reductase degradation protein 1; Keap1, kelch-like ECH-associated protein 1; NQO1, NAD(P)H quinone oxidoreductase 1; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; SOD2, superoxide dismutase 2; sMaf, small Maf proteins.

the NF-κB signaling pathway serves as the central mediator that links redox imbalance to inflammatory responses. In chronic liver diseases, such as alcoholic liver disease, NAFLD, viral hepatitis and cholestatic liver disease, NF-κB remains persistently activated, with its activity level influencing disease progression (48,49). Under basal conditions, NF-κB is sequestered in the cytoplasm by IκB protein. Upon cellular stimulation, such as via ROS, IκB is phosphorylated and degraded, freeing NF-κB to translocate into the nucleus and subsequently initiate the transcription of target genes. Activated NF-κB upregulates pro-inflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and toll-like receptors (TLRs), thereby triggering and amplifying inflammatory responses (50-52). This subsequently results in a cycle of oxidative stress and inflammatory responses, and this cycle plays a notable role in the pathological progression of liver injury (53) (Fig. 3).

Given the notable role of NF-κB in hepatic inflammation, targeting this pathway has become an important strategy in the treatment of liver diseases. Multiple studies have demonstrated that inhibiting NF-κB activity can effectively alleviate liver damage. For instance, in an acetaminophen (APAP)-induced acute liver-injury model, aloperine has been shown to mitigate liver damage by suppressing the TLR4/NF-κB signaling pathway, thereby blocking NF-κB-mediated activation of the NLR family pyrin domain containing 3 inflammasome (54). Further research has shown that taraxasterol modulates both the Nrf2/HO-1 and NF-κB pathways in ethanol-induced liver injury models, concurrently enhancing antioxidant capacity and suppressing inflammatory responses, thereby regulating oxidative stress and inflammatory cascades to break the cycle between oxidative stress and inflammation (51).

Notably, the sustained activation of NF-κB can induce chronic inflammatory responses, whereas excessive or untimely inhibition of NF-κB has been shown to impair hepatocyte survival, liver regeneration and immune defense (48,55). During liver regeneration, transient and moderate NF-κB activation is important for the orderly progression of the hepatocyte cell cycle and hepatic tissue repair (56). Conversely, the inhibition of NF-κB signaling markedly increases the susceptibility of hepatocytes to TNF-α-mediated apoptosis, and this apoptotic injury consequently delays hepatic functional recovery (57). In addition, basal NF-κB activity is important for the capacity of the liver to defend against pathogenic invasion and maintain immune homeostasis. Animal experiments have demonstrated that mice with defective NF-κB activation in hepatocytes display a high susceptibility to bacterial infections (58). Accordingly, elucidating the functional balance of NF-κB under distinct pathophysiological contexts is important for developing therapeutic strategies for liver diseases targeting this signaling pathway.

Oxidative stress-induced hepatocyte apoptosis pathways and molecular regulatory mechanisms. Hepatocyte apoptosis has been recognized as a central pathological event contributing to tissue dysfunction and structural damage in a number of liver diseases, including viral hepatitis, alcoholic liver disease, NAFLD, cholestasis and I/R injury (59). Hepatocyte apoptosis proceeds via two pathways. The extrinsic death receptor pathway is triggered by death ligands, such as TNF-α, binding to membrane receptors, which activates caspase-8. The

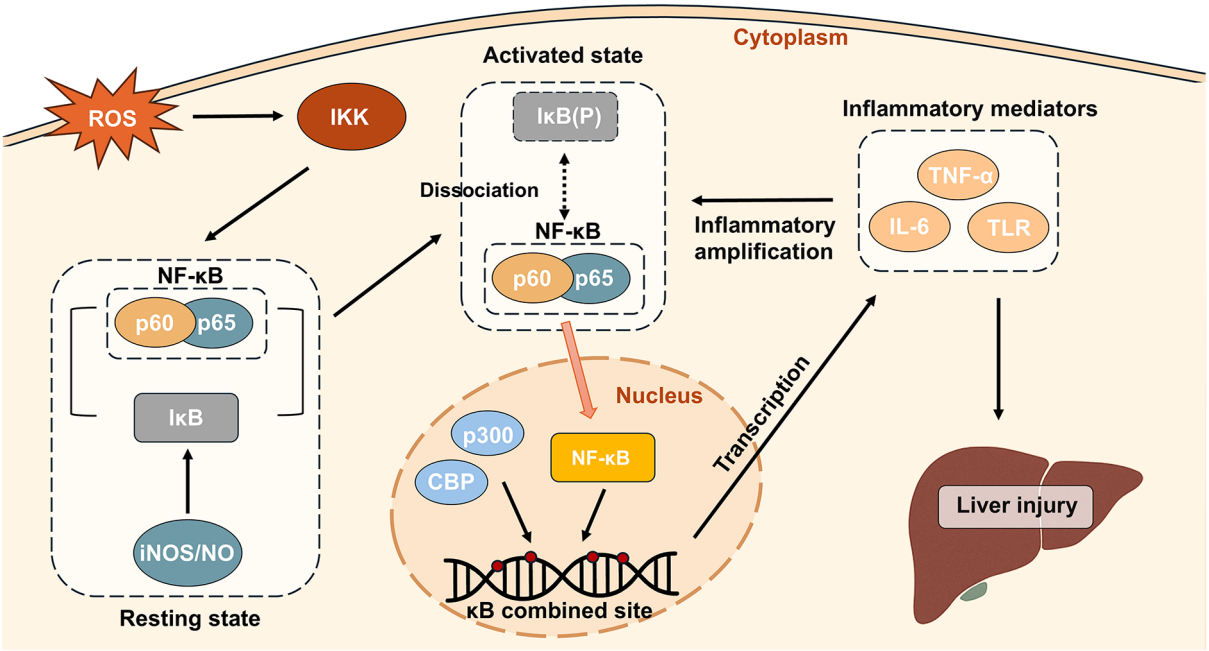

Figure 3. Core pathological mechanism of the NF-κB signaling pathway in oxidative stress-induced liver inflammation. Under resting conditions, NF-κB is sequestered in the cytoplasm by binding to its endogenous inhibitor, IκB. Oxidative stress activates the IKK complex, leading to IκB phosphorylation and degradation. Released NF-κB translocates to the nucleus, where it initiates the transcription of key pro-inflammatory mediators, such as TNF-α and IL-6. CBP, CREB-binding protein; IKK, IκB kinase; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor-κB; NO, nitric oxide; p50, NF-κB subunit p50; p65, NF-κB subunit p65; ROS, reactive oxygen species; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; IκB(P), IκB phosphorylation.

intrinsic mitochondrial pathway, which is initiated by intracellular stresses, such as oxidative stress, modulates the balance of the B-cell lymphoma (Bcl)-2 protein family, induces permeabilization of the mitochondrial outer membrane and cytochrome c release, and activates caspase-9. Both pathways ultimately converge on the activation of caspase-3, which irreversibly executes the apoptotic program (Fig. 4) (60,61). Notably, during liver injury progression, apoptosis acts as an important downstream effector in the combined action of oxidative stress and inflammation by further exacerbating local inflammation and oxidative stress levels, thereby forming a recurring cycle (62).

Various bioactive substances exert hepatoprotective effects by targeting key nodes in apoptotic pathways. *Paeonia lactiflora* Pall. has been shown to exert anti-apoptotic hepatoprotective effects in APAP-induced liver injury by inhibiting ERK phosphorylation, which stabilizes mitochondrial membrane permeability and blocks the release of mitochondrial apoptotic signals (63). In addition to directly targeting apoptotic signaling molecules, interventions targeting the upstream regulatory links of oxidative stress and apoptosis have also exhibited promising hepatoprotective potential. In acute alcoholic liver injury, procyanidin B2 has been shown to inhibit aberrant PI3K/Akt/NF-κB activation to attenuate oxidative stress, inflammation and hepatocyte apoptosis (64). Furthermore, *Tridax procumbens* leaf extract has been shown to activate the Nrf2 pathway to reverse cellular redox imbalance, consequently inhibiting hepatocyte apoptosis triggered by chemotherapeutic drug-induced oxidative damage (65). Therefore, apoptosis represents a critical effector mechanism through which oxidative stress contributes to hepatocyte injury. Collectively, these findings demonstrate that pharmacological interventions targeting apoptotic pathways can effectively inhibit hepatocyte apoptosis and thereby delay the progression of liver injury, whether through direct inhibition of apoptotic signaling or through upstream regulation of oxidative stress. This has provided potential novel strategies for the targeted therapy of liver diseases.

Summary. In summary, oxidative stress is a core pathological factor that underlies the initiation, progression and malignant transformation of liver injury. It not only directly modifies biological macromolecules, including lipids, proteins and DNA, but also modulates three core signaling axes, the Nrf2, NF-κB and apoptosis signaling pathways. This establishes a cycle of mutual reinforcement between oxidative imbalance, the inflammatory cascade and apoptosis, which forms the pathological foundation of acute and chronic liver diseases.

Notably, the Nrf2, NF-κB and apoptosis pathways exert dual regulatory roles in liver injury, and their functional effects have been closely associated with disease progression, the intensity of their activation and other relevant factors. Nrf2-driven antioxidant defense mitigates acute hepatic oxidative damage, but chronic aberrant activation promotes liver cancer progression, immune escape and chemoresistance (41). Meanwhile, sustained NF-κB activation, a core mediator of oxidative stress and inflammation, aggravates chronic liver inflammation and fibrosis, whereas its transient physiological activation supports liver regeneration and immune homeostasis. Physiologically, apoptosis clears damaged cells to maintain tissue homeostasis, but its overactivation inflicts irreversible parenchymal injury and amplifies oxidative and inflammatory cascades. Furthermore, these three pathways do not mediate the pathological process independently. They cross-regulate

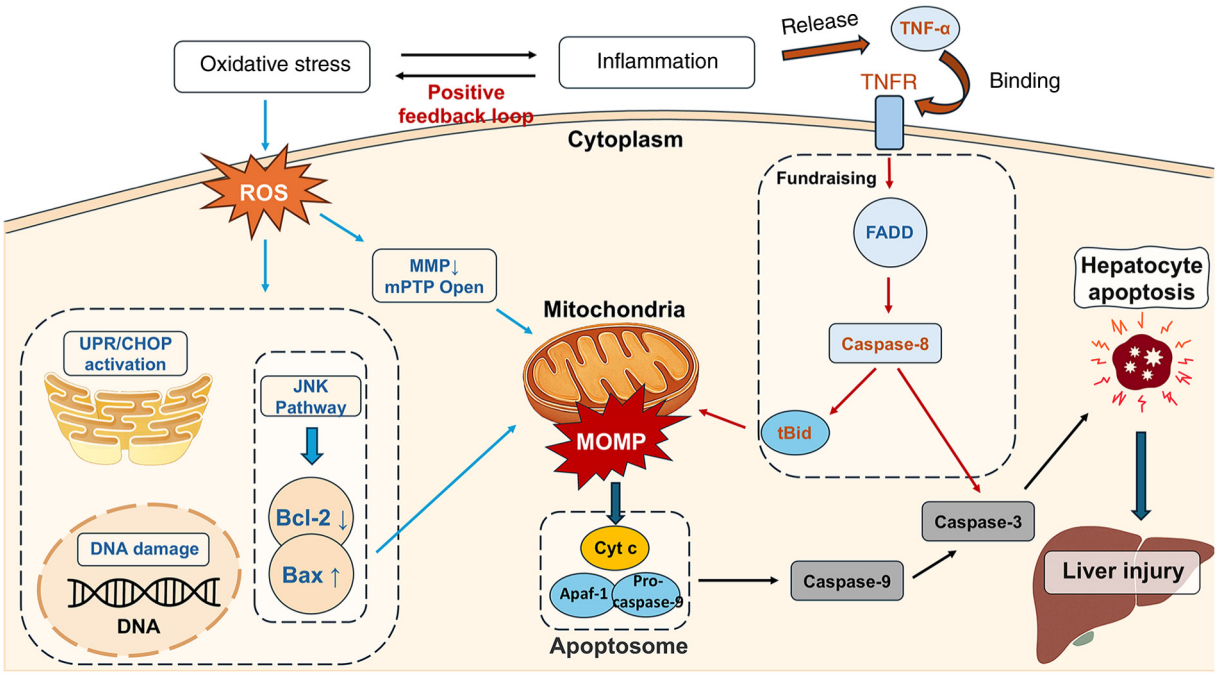

Figure 4. Apoptosis constitutes a central pathological process that executes tissue destruction in oxidative stress-induced liver injury. Oxidative stress predominantly activates the intrinsic mitochondrial pathway by modulating the balance of Bcl-2 protein family, leading to mitochondrial Cyt c release and caspase-9 activation. Oxidative stress can also engage the extrinsic death receptor pathway, for example via TNF-α, which activates caspase-8. Both pathways converge to activate the executioner caspase-3, irreversibly committing the hepatocyte to apoptosis. Apaf-1, apoptotic protease activating factor-1; CHOP, C/EBP homologous protein; Cyt c, cytochrome c; FADD, Fas-associated death domain; JNK, c-Jun N-terminal kinase; MMP, mitochondrial membrane potential; MOMP, mitochondrial outer membrane permeabilization; mPTP, mitochondrial permeability transition pore; tBid, truncated Bid; TNF-α, tumor necrosis factor-α; TNFR, tumor necrosis factor receptor; UPR, unfolded protein response; ROS, reactive oxygen species; Bcl-2, B-cell lymphoma-2.

one another to form an integrated signaling network, which underlies the limited efficacy of single-target clinical interventions (60). The natural flavonoid rutin, a dietary flavonoid with well-established antioxidant and anti-inflammatory properties, is considered a promising candidate for multi-target modulation of the aforementioned signaling pathways (66). The present review discusses the hepatoprotective mechanisms of rutin across diverse liver-injury models, starting with its structural and pharmacological fundamentals.

3. The chemical structure and antioxidant properties of rutin

Basic chemical structure of rutin. Rutin, a naturally occurring flavonoid, is widely distributed across various plants. Its chemical structure consists of the flavonoid aglycone quercetin linked via a glycosidic bond to a disaccharide group composed of glucose and rhamnose. The quercetin moiety of rutin contains two benzene rings and multiple hydroxyl groups, which are characteristic of the 3',4'-dihydroxyphenyl and 5,7-dihydroxyflavone skeletons. Rutin exhibits the molecular formula $C_{27}H_{30}O_{16}$ and a molecular weight of 610.51 g/mol (12,67,68). These hydroxyl groups confer notable antioxidant activity, enabling rutin to effectively scavenge superoxide, peroxyl and hydroxyl radicals and form complexes with transition metals, for example iron and copper, thereby enhancing its antioxidant and anti-inflammatory effects (69-71). The glycosyl groups, particularly glucose linked to rhamnose via α-1,6 bonds, markedly impact the solubility and bioavailability of rutin, making these groups important for pharmaceutical formulations and bioavailability studies using rutin (67,68). *In vivo*, rutin is metabolized into glucuronic acid, sulfate and methylated derivatives. The plasma elimination half-life of rutin is 12-19 h (72). Thus, the bioactivity of rutin results not only from the free-radical scavenging ability of the hydroxyl groups on the quercetin aglycone but also from the modulation of the metabolic stability and bioaccessibility of rutin via its glycosylation. This unique structural feature enables rutin to exhibit broad biological activities, including antioxidation, anti-inflammation and metal chelation, demonstrating notable potential for various applications (69,70).

Antioxidant pharmacological effects of rutin. The mechanism of action of rutin encompasses multiple aspects, including antioxidative and anti-inflammatory effects, as well as signaling pathway regulation. Its antioxidant effects form the foundation for its broad pharmacological activities, particularly in liver protection.

In the liver, rutin mitigates oxidative damage and lipid peroxidation in hepatocytes primarily through the direct scavenging of free radicals, the chelation of transition metal ions and the upregulation of endogenous antioxidant defense systems, for example superoxide dismutase (SOD) and glutathione (GSH) (73). This mechanism of action has shown promise in treating metabolic liver diseases such as NAFLD, improving insulin resistance, delaying the progression of liver fibrosis and providing adjunctive strategies for drug-induced liver injury (27). Regarding neurodegenerative diseases, rutin has been shown to enhance cognitive function in patients with Alzheimer's disease and Parkinson's disease

via mechanisms involving the reduction of amyloid protein deposition, inhibition of oxidative stress and suppression of inflammatory factors (74,75). In cardiovascular diseases, rutin has been shown to inhibit macrophage-mediated inflammatory responses and foam-cell formation, promote autophagy and modulate the PI3K/Akt pathway, thus slowing the progression of atherosclerotic plaques (76). Additionally, rutin has been shown to scavenge free radicals, reduce lipid peroxidation and enhance endogenous antioxidant enzyme activity, thereby lowering oxidative stress and preserving vascular function. These effects contribute to protection against myocardial ischemia and exhibiting therapeutic effects in patients with hypertension (73,77). Rutin has been shown to suppress the high-mobility group protein B1/TLR4/MYD88/NF-κB innate immune axis and reduce inflammatory and oxidative stress markers in ulcerative colitis, thereby alleviating colonic mucosal damage and exerting anti-inflammatory and immunomodulatory effects (78).

The pharmacological actions of rutin involve the specific modulation of several key signaling pathways. Rutin activates the Nrf2/ARE pathway to enhance cellular antioxidant defenses and concurrently suppresses NF-κB pathway activation and downstream pro-inflammatory gene expression, mediating anti-inflammatory responses. Additionally, rutin influences apoptotic processes by modulating the caspase cascade and the balance of Bcl-2 family proteins (Fig. 5) (66). Given the central role of oxidative stress and inflammation in liver diseases, these notable antioxidant, anti-inflammatory and cytoprotective properties form the basis of the therapeutic potential exhibited by rutin in a range of liver diseases. The following section further explores the specific protective effects and mechanisms of rutin in various liver-injury models.

4. Study on the hepatoprotective mechanism of rutin based on oxidative stress regulation

Rutin and chemical liver injury. In chemical-induced liver injury, the protective effects of rutin have been demonstrated by notable improvements in a range of physiological and biochemical indicators after treatment, providing direct evidence of its therapeutic efficacy. For example, a previous study has shown that rutin effectively inhibits the increase in serum transaminase activities, particularly those of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), induced by CCl_4 in rats, highlighting its hepatoprotective properties (79). In a rat model of CCl_4-induced liver injury, rutin has been shown to exert hepatoprotective effects via its antioxidant activity, reversing elevated serum liver-injury markers, restoring hepatic endogenous antioxidant defenses and ameliorating lipid peroxidation, DNA damage and hepatic histopathological lesions (80). Molecular and histological evidence has further indicated that rutin reduces the mRNA expression levels of poly(ADP-ribose) polymerase-1 and vascular endothelial growth factor, alleviates tissue damage and promotes tissue repair (81). In CCl_4- and thioacetamide-induced rat hepatotoxicity models, rutin has been shown to mitigate DNA fragmentation and 8-oxo-2'-deoxyguanosine damage and to markedly ameliorate histopathological liver changes (82,83). Beyond its protection against chemical liver injury, long-term rutin administration enhances antioxidant defense capacity in healthy animals. For example, a study has shown that rutin administration inhibits ROS accumulation in HepG2 cells and improves redox imbalance-related indicators in mouse models of oxidative stress (84).

These notable phenotypic improvements have been primarily attributed to the capacity of rutin to modulate key hepatic oxidative stress pathways. Rutin exerts hepatoprotective effects through the regulation of important signaling pathways, including the mitogen-activated protein kinase (MAPK), NF-κB and Nrf2 pathways. In response to chemical toxin-induced injury, rutin first enhances antioxidant defense by activating the Nrf2/ARE pathway, thereby promoting Nrf2 nuclear translocation and the activation of the ARE, which in turn boosts the activity of downstream antioxidant enzymes and mitigates oxidative stress damage (12,85). However, oxidative stress induced by chemical toxins can rapidly trigger downstream inflammatory and apoptotic cascades (86,87). Consequently, the hepatoprotective effects of rutin are also reflected in its regulation of the core inflammatory pathway: The NF-κB signaling pathway. Rutin inhibits pathological NF-κB overactivation by modulating upstream signal transduction. For example, rutin has been shown to alleviate zearalenone-induced hepatic inflammation and intestinal barrier dysfunction in mice by modulating the gut microbiota, improving intestinal barrier function and reducing the production and leakage of lipopolysaccharides, thereby inhibiting the aberrant activation of the NF-κB pathway (88). In cadmium-induced liver injury, rutin has been shown to indirectly suppress NF-κB activation by regulating the upstream MAPK signaling pathway. Specifically, rutin reduces the phosphorylation of key MAPK proteins, such as ERK, c-Jun N-terminal kinase (JNK) and p38, thereby decreasing NF-κB activity and suppressing the release of pro-inflammatory cytokines (89). The rutin-mediated inhibition of p38α MAPK has been shown to interfere with the nuclear translocation of NF-κB and its coactivator Bcl-3, suppressing the transcriptional expression of inflammatory mediators, such as TNF-α and IL-1β (90).

Furthermore, rutin has been shown to suppress NF-κB-driven inflammatory responses in multiple chemical-induced liver-injury models, as well as to block apoptotic cascades. Rutin has been shown to suppress the NF-κB-mediated inflammatory cascade in deltamethrin-induced liver-injury models, reducing the levels of pro-inflammatory factors and inflammatory mediators. In these models, rutin has also been shown to block the apoptotic cascade by regulating the Bcl-2/Bax and caspase-3 pathways (12,81). Similarly, rutin has been shown to reduce the expression of genes induced by perfluorooctanoic acid, such as TNF-α, IL-6, NF-κB and JNK, alleviating inflammatory responses (19). In terms of anti-apoptotic effects, rutin influences the NF-κB signaling pathway to inhibit the expression of caspase-3 (91). Notably, the dual ability of rutin to activate the Nrf2 pathway and inhibit the NF-κB pathway effectively counteracts the cycle of oxidative damage, inflammation and apoptosis caused by chemical-induced liver injury, reversing λ-cyhalothrin-induced oxidative stress and apoptosis in liver-injury models (85).

In summary, chemical-induced liver injury is directly triggered by exogenous toxins causing severe oxidative stress, and rutin initiates its therapeutic activity by modulating the

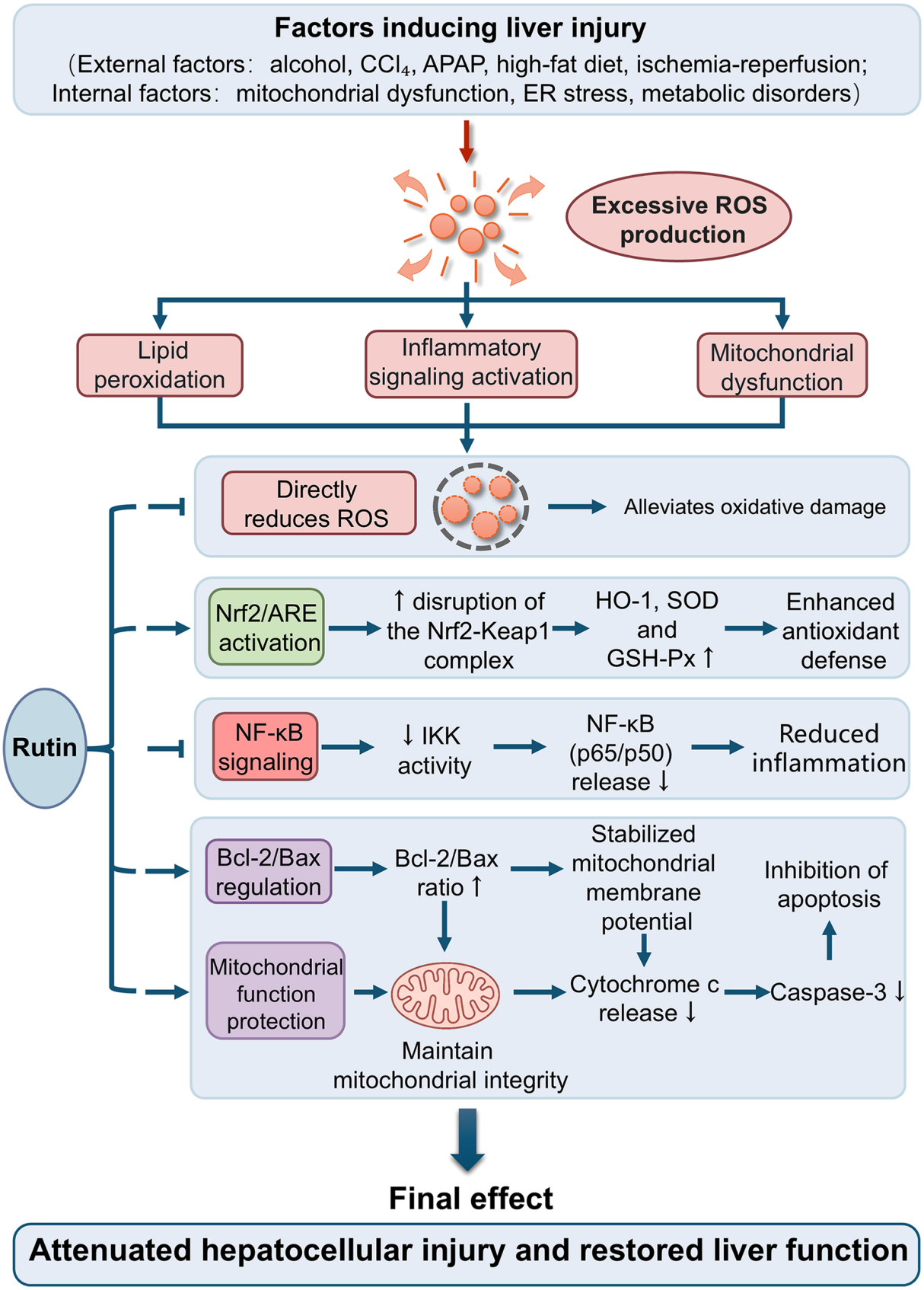

Figure 5. Schematic of the hepatoprotective mechanisms of rutin. Exogenous and endogenous stimuli induce excessive ROS generation, leading to lipid peroxidation, inflammatory signaling and mitochondrial dysfunction. Rutin: i) Directly scavenges ROS; ii) activates the Nrf2/ARE pathway, which disrupts Nrf2/Keap1 signaling and upregulates HO-1, SOD and GSH-Px; iii) inhibits NF-κB signaling, reducing IKK activity and p65/p50 release; and iv) protects mitochondria, increasing the Bcl-2/Bax ratio, stabilizing membrane potential and suppressing caspase-3. These actions enhance antioxidant defense, reduce inflammation, inhibit apoptosis and ultimately attenuate liver injury and restore liver function. ROS, reactive oxygen species; ARE, antioxidant response element; Bcl-2, B-cell lymphoma-2; GSH-Px, glutathione peroxidase; HO-1, heme oxygenase-1; IKK, IκB kinase; Keap1, kelch-like ECH-associated protein 1; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2-related factor 2; SOD, superoxide dismutase; ER, endoplasmic reticulum; APAP, acetaminophen.

Nrf2-mediated endogenous antioxidant system. Rutin then coordinately regulates and blocks subsequent inflammatory and apoptotic cascade reactions through multiple pathways, ultimately reversing the molecular and tissue-level liver damage induced by chemical toxins.

Rutin and drug-induced liver injury. The core mechanism of drug-induced liver injury is excessive oxidative stress triggered by drug metabolism. Rutin effectively ameliorates drug-induced liver injury, with therapeutic effects manifested through improvements at the biochemical, physiological and histopathological levels. A study has shown that after rutin intervention, abnormal serum transaminase levels, such as ALT and AST, are markedly reduced, and oxidative stress, inflammatory factors, DNA damage and tissue injuries are mitigated (92). For example, rutin has been shown to alleviate histopathological liver damage induced by methotrexate, including hepatic inflammatory infiltration, hepatocyte vacuolation, and sinusoidal dilation and congestion (93).

Rutin exerts hepatoprotective effects by regulating oxidative stress-related signaling pathways. In two representative drug-induced liver-injury models, including the doxorubicin- and vortioxetine-induced rat models, rutin has markedly alleviated hepatic oxidative damage via activation of the Nrf2 signaling pathway. Specifically, rutin has been shown to activate Nrf2 to regulate the AREs, thereby upregulating the activity of antioxidant enzymes, such as SOD, GSH and GSH S-transferase. This has been shown to enhance antioxidant defenses and clear excessive ROS, alleviating doxorubicin- and vortioxetine-induced hepatotoxicity in rats (92,94).

Accumulating evidence has suggested that, in addition to alleviating oxidative stress by promoting the endogenous antioxidant defense system, rutin may reduce lipid peroxidation and suppress the release of pro-inflammatory factors, such as TNF-α, via inhibiting the NF-κB signaling pathway, thus mitigating drug-triggered inflammatory responses (95,96). Furthermore, rutin synergistically reduces hepatic oxidative damage and inflammation through coordinated regulation of NF-κB and MAPK pathways. In a cyclophosphamide (CP)-induced hepatitis model, rutin has been shown to alleviate the oxidative-inflammatory cascade triggered by ROS and TNF-α by downregulating the expression of p38 MAPK and NF-κB, suppressing their downstream effector molecules, such as cyclooxygenase-2 and inducible nitric oxide (NO) synthase (iNOS) (97).

The protective mechanisms exhibited by rutin also extend to oxidative stress-related apoptotic pathways. A study has shown that rutin reduces ROS production by inhibiting thioredoxin-interacting protein activity and promoting its degradation, thus suppressing apoptosis signal-regulating kinase 1 activation and its downstream apoptotic signaling pathways. This mitigates mitochondrial damage and cellular apoptosis (98).

In summary, the hepatoprotective effects of rutin against drug-induced liver injury are achieved through multi-target and multi-pathway synergistic regulation of oxidative cascade reactions, with the Nrf2 pathway serving as the core antioxidant axis complemented by other pathways to counteract oxidative stress and inflammation caused by drug metabolism, thereby maintaining and restoring hepatocyte homeostasis. This not only provides a theoretical foundation for further research into the hepatoprotective mechanisms of rutin but also offers valuable insights for developing clinical adjuvant therapeutic strategies for mitigating chemotherapy-induced liver injury.

Rutin and metabolic dysfunction-associated steatotic liver disease (MAFLD). Unlike chemical- and drug-induced liver injuries caused by exogenous substances, metabolic factor-associated liver injury arises from chronic imbalances in energy metabolism (99). Although its triggers are varied, the subsequent pathological processes are closely linked to hepatocyte damage, inflammatory responses and oxidative stress (100). The therapeutic effects of rutin on this type of liver injury are manifested through its pleiotropic actions, which include regulating lipid metabolism, improving insulin resistance and exerting potent antioxidant and anti-inflammatory properties, thus halting liver damage progression. Rutin also directly modulates lipid and glucose metabolic signaling pathways, thereby addressing the root cause of metabolic disorders (27).

In a high-fat diet-induced mouse model of MAFLD, rutin has been shown to notably reduce body weight and hepatic steatosis. Rutin has also been shown to lower blood levels of total cholesterol, low-density lipoprotein, triglycerides, free fatty acids and lipid droplet accumulation, as well as to increase high-density lipoprotein cholesterol levels and alleviate hepatic lipid accumulation (27,101). These metabolic improvements have been attributed to the capacity of rutin to regulate metabolism-related signaling pathways. Specifically, rutin activates the 5'-AMP-activated protein kinase (AMPK) pathway to inhibit sterol regulatory element-binding protein 1-driven lipogenesis and mitigate oxidative stress through the downstream Nrf2 axis (102); this regulatory effect has been corroborated by studies of rutin-rich herbal extracts against hepatic steatosis (103). Simultaneously, rutin restores the activity of peroxisome proliferator-activated receptor-α and its downstream target carnitine palmitoyltransferase 1/2 to facilitate fatty acid metabolism and suppress lipogenesis (104). A related study has also indicated that rutin-rich herbal materials exert similar hepatoprotective effects via antioxidant pathways (104). Notably, rutin has also been shown to effectively improve insulin resistance in a type 2 diabetes-related liver injury model By promoting the activation of insulin receptor substrate 2 and subsequently activating the PI3K/Akt/GSK-3β signaling pathway, rutin reduces blood glucose levels and decreases the production of advanced glycation end-products, providing hepatic protection under type 2 diabetic conditions (105).

In MAFLD, the pathological progression from lipid accumulation to hepatic injury is largely driven by oxidative stress and inflammation. In addition to its regulatory effects on lipid metabolism, rutin has been shown to alleviate MAFLD-related hepatic damage through its antioxidant and anti-inflammatory properties. Specifically, rutin treatment has been shown to restore serum transaminase levels, including AST and ALT; enhance endogenous antioxidant enzyme activities, such as SOD and GSH peroxidase; and reduce lipid peroxidation markers, such as malondialdehyde (MDA) in experimental models of MAFLD (18,106). Specifically, in a rat model of metabolic syndrome, rutin has been shown to reverse or prevent

pathological metabolic changes, such as increased abdominal fat and impaired glucose tolerance, alleviate abnormalities in liver structure and function, and reduce oxidative stress and inflammation in the liver (107). At the molecular level, rutin inhibits the NF-κB pathway, suppressing the expression and release of inflammatory factors, such as TNF-α and IL-1β. Rutin also activates the Nrf2 pathway, leading to the upregulation of its downstream antioxidant targets, including HO-1 and NAD(P)H quinone oxidoreductase 1, to enhance the antioxidant defense capacity of the body, synergistically mitigating oxidative and inflammatory damage in MAFLD (84). Additionally, rutin inhibits the cytochrome P450 2E1 and JNK1 pathways, reducing ROS generation at the source and downregulating the expression of inflammatory mediators, such as iNOS, thereby breaking the cycle of oxidative stress and inflammation (106).

Rutin derivatives have also shown promise in treating MAFLD. Troxerutin has been shown to alleviate metabolic syndrome-related pathologies in high-fat diet-fed mice by reducing hepatic steatosis, enhancing fatty acid oxidation and inhibiting oxidative stress-mediated NAD depletion and endoplasmic reticulum stress (108). Furthermore, sodium rutin has been shown to modulate gene expression to promote fatty acid β-oxidation and reduce hepatic steatosis (104,108).

Notably, rutin also exhibits iron-chelating properties, offering a unique mechanism for treating liver diseases linked to iron metabolism disorders. A study has indicated that hepatic iron overload is an independent risk factor for MAFLD progression and insulin resistance. In a metabolic-disorder model, rutin treatment has been shown to markedly reduce hepatic ferritin expression and serum transferrin saturation, as well as to increase serum unsaturated iron-binding capacity. This suggests that rutin can chelate excess free iron, regulate hepatic iron metabolism and effectively inhibit the iron-catalyzed Fenton reaction, thereby suppressing ROS production at the source. Consequently, rutin has emerged as a potential iron chelator, showing promise not only for treating iron overload-related liver diseases, such as transferrin receptor protein 2-deficient type 3 hereditary hemochromatosis (109), but also offering an additional novel approach to alleviating oxidative stress in MAFLD.

In summary, in more complex cases of metabolism-related liver injury, rutin demonstrates multi-faceted regulatory capabilities. Rutin achieves synergistic modulation of liver-injury progression through multiple mechanisms, including metabolic-disorder correction, insulin-resistance amelioration and oxidative-stress suppression, rather than solely regulating the oxidative-stress cascade. Consequently, rutin serves as a natural hepatoprotective agent against liver injuries induced by various pathological factors.

Rutin and alcoholic liver disease. The core mechanism of alcoholic liver disease involves oxidative stress, lipid metabolism disorders and gut microbiota dysbiosis, all triggered by ethanol and its metabolites (110). The hepatoprotective mechanism of rutin is achieved through multi-pathway interventions within this complex pathological network.

Studies have shown that rutin can effectively reverse ethanol-induced hepatic steatosis, reducing lipid accumulation in the liver. For example, rutin has markedly lowered serum transaminase levels, such as AST and ALT, and hepatic triglyceride content in alcohol-fed mice and concurrently suppressed the expression of fatty acid synthase and acetyl-coA carboxylase, resulting in reduced hepatic lipid accumulation (111). This effect has been further validated at the cellular level, as rutin has been shown to alleviate ethanol-induced toxicity in HepG2 cells, improving cell membrane integrity, notably reducing intracellular lipid droplet accumulation under ethanol exposure and markedly enhancing cell viability (112,113). In terms of antioxidant effects, rutin has been shown to markedly increase the activity of antioxidant enzymes, for example SOD and catalase (CAT), and downregulate thiobarbituric acid reactive substances expression, effectively inhibiting ethanol-induced oxidative stress and lipid peroxidation (111).

Furthermore, rutin ameliorates alcoholic liver disease by modulating key pathways related to hepatic lipid metabolism. A study has shown that tartary buckwheat extract containing abundant rutin modulates glycerophospholipid metabolism and the phosphatidylcholine/ phosphatidylethanolamine balance to restore hepatic lipid transport and exerts protective effects against alcohol-triggered oxidative stress (114). In terms of antioxidant effects, rutin has been shown to alleviate alcohol-induced oxidative stress and inflammation in HepG2 cells by activating the Nrf2/ARE pathway and enhancing the expression of antioxidant enzymes, such as SOD and CAT (115). Additionally, rutin has been shown to restore the dynamic balance of mitochondrial homeostasis by inhibiting the expression of the key mitochondrial fission protein dynamin-related protein 1, mitigating ethanol-induced oxidative damage at the organelle level (112). Furthermore, rutin is also an important active constituent of multiple herbal tea extracts. A previous study has shown that rutin-rich plant extracts can upregulate hepatic alcohol-metabolizing enzymes, and that these extracts alleviate alcoholic liver damage by regulating gut microbiota and maintaining intestinal homeostasis via the gut-liver axis (116).

Notably, bioavailability is important for the efficacy of rutin treatment. Tartary buckwheat flour extracts enriched with rutin have exhibited notable therapeutic effects in ethanol-induced liver injury in rats due to superior oral absorption and prolonged blood retention time compared with rutin alone (117). Similarly, *Dendropanax morbiferus* leaf extracts rich in rutin has been shown to prevent alcoholic liver injury by efficiently scavenging alcohol-generated ROS (118). In summary, rutin protects against alcohol-induced liver injury through multi-target and multi-pathway synergism, with its core mechanism of action centered on counteracting alcohol-induced oxidative stress and correcting oxidative stress-induced inflammatory responses and lipid metabolism disorders.

Rutin and other types of liver injury. In addition to common liver injuries, rutin has shown potential in treating less common pathological models, such as hepatic I/R injury and cholestatic liver injury models. Unlike toxins, drugs or metabolic disorders that directly damage the liver, hepatic I/R injury is surgery-related and is characterized by acute oxidative bursts and microcirculatory disturbances (119). Cholestatic liver injury, on the other hand, is marked by chronic inflammation, bile duct reactions and fibrosis (120). Studies have provided

supportive evidence that rutin exerts notable protective effects against both of these distinct types of liver injury, highlighting its unique advantage in multi-target pharmacological action.

Rutin and hepatic I/R injury. Hepatic I/R injury is a leading cause of liver failure after transplantation and hepatectomy, with oxidative stress and microcirculatory disturbances being the primary pathological mechanisms behind this injury type (119). Rutin protects the liver against I/R-induced local injury through direct free-radical scavenging, inhibition of lipid peroxidation and restoration of endogenous GSH reserves (121). Its protection against remote organ damage is primarily attributed to the preservation of microcirculatory function and the reduction of neutrophil infiltration into distant tissues (122). Specifically, rutin preconditioning has been shown to markedly reduce blood MDA levels, inhibit lipid peroxidation and restore total GSH levels, thereby enhancing endogenous antioxidant reserves (121). In terms of anti-inflammatory effects, rutin has been shown to suppress myeloperoxidase activity, alleviate neutrophil cytotoxicity, reduce tissue inflammatory infiltration and ultimately mitigate neutrophil-mediated tissue injury (121). In a rat model of hepatic I/R, rutin modulates the dimethylarginine dimethylaminohydrolase (DDAH)/asymmetric dimethylarginine/NOS axis by counteracting DDAH1 upregulation, inhibiting iNOS and enhancing endothelial NOS to correct NO imbalance and improve microcirculation. Rutin also restores depleted thiol groups, reinforcing antioxidant defenses, thereby alleviating hepatic I/R injury (20).

Rutin and cholestatic liver injury. Rutin has demonstrated notable protective effects against cholestatic liver injury, which is characterized by inflammation, fibrosis and bile duct reactions. Rutin has been shown to exert multi-faceted protective actions, ranging from hepatocyte protection to the amelioration of biliary fibrosis. A study has indicated that rutin not only reduces serum levels of AST and ALT, alleviating hepatocyte degeneration and necrosis, but also inhibits bile duct hyperplasia, decreases collagen expression and reduces collagen deposition in liver tissue, improving the structural disorganization induced by cholestasis (123). From the perspective of signaling pathway regulation, rutin has been shown to exert hepatoprotective effects through multi-pathway synergistic actions. Rutin has been shown to inhibit the phosphorylation of ERK, blocking the downstream NF-κB inflammatory signaling pathway and the TGF-β/Smad fibrotic signaling pathway, thus reducing the synthesis of pro-inflammatory factors and collagen (124). Furthermore, rutin has been shown to activate the Nrf2/HO-1 antioxidant signaling axis, enhance antioxidant enzyme activity and promote AMPK phosphorylation, collectively mitigating oxidative damage. The synergistic activity of these pathways ultimately targets α-smooth muscle actin$^+$ myofibroblasts, inhibiting their activation while alleviating oxidative stress and reducing the activation triggers of these cells, thereby suppressing liver fibrosis at the cellular level (123,125).

In summary, the hepatoprotective effects of rutin do not rely on the regulation of a single pathway but stem from its multi-directional, synergistic modulation of the hepatic cell signaling network. Whether in response to exogenous toxins or drugs, metabolic disorders, cholestasis or ischemia-induced stress reactions, rutin precisely targets the core mechanism of oxidative stress and subsequent inflammation and synergizes with other pathways to effectively alleviate or reverse liver injury. Notably, all evidence summarized in the present review is solely derived from preclinical studies, including animal model experiments and *in vitro* assays, with no involvement of human clinical trials. This is systematically reflected in Table I (12,18-20,79-85,88-94,97,98,102,105-109,111-113,115,117,121,123), which provides an overview of the antioxidant effects of rutin in various liver injury models in preclinical studies. The capacity of rutin to integrate multiple pathways with multiple effects not only explains the applicability of rutin in various liver injury models but also suggests the potential of rutin as a broad-spectrum hepatoprotective agent, particularly in clinical treatments, such as chemotherapy adjuvant therapy.

5. Nano-application prospects of rutin in liver injury

Pharmacokinetic studies are important for determining drug bioavailability. Traditional drug delivery technologies often exhibit poor responsiveness to changes in metabolic and pathological states, failing to achieve targeted drug delivery and enhance bioavailability (126-128). For example, although short-chain fatty acids (SCFAs) have shown therapeutic potential in the treatment of non-alcoholic steatohepatitis (NASH), their low molecular weight and high water solubility lead to unfavorable pharmacokinetic properties, resulting in rapid systemic clearance that limits therapeutic efficacy and may also cause adverse effects (129).

Notably, advances in nanomaterial synthesis and application have provided novel solutions for disease treatment. The liver, a key organ of the reticuloendothelial system, efficiently captures nanoparticles from the bloodstream after intravenous administration, promoting their accumulation in the liver. Consequently, antioxidant nanocatalysts with passive liver-targeting capabilities and catalytic antioxidant properties are ideal candidates for treating liver injury (130). A study has shown that constructing SCFAs into self-assembled pro-drug nanomicelles (NanoBAs) successfully extends the effective retention time of SCFAs in the liver from <24 to 72 h. Furthermore, NanoBAs have demonstrated superior anti-fibrotic effects and reduced lipid deposition compared with traditional SCFA-based formulations in a NASH mouse model (129). Rutin, a natural flavonoid compound, has shown notable potential in treating various types of liver injury. However, its poor water solubility and notable first-pass effect result in markedly low oral bioavailability (~3.6%), which severely limits its clinical efficacy (126).

To overcome this limitation, several previous studies have explored nanotechnology-based delivery systems for rutin. For example, rutin nanoemulsions have been successfully developed to enhance intestinal absorption, bypass the first-pass effect and markedly increase relative bioavailability compared with rutin suspension, with a reduction in peak concentration time from 4 to 2 h, thereby markedly improving the therapeutic efficacy of rutin (126). Another study has utilized the hydroxyl groups and glycosidic bonds in rutin to form coordination bonds with cerium ions, thereby combining quercetin and mannitol to construct coordination polymer D-mannitol-cerium-quercetin/rutin coordination polymer

Table I. Overview of the antioxidant effects of rutin in various liver injury models in preclinical studies.

A, Chemical liver injury

First author, year	Liver disease type	Experimental models	Rutin dose (administration, frequency)	Therapeutic mechanism	(Refs.)
Janbaz *et al*, 2002	Paracetamol- and CCl_4-induced hepatotoxicity	Swiss male mice and Wistar male rats	20 mg/kg (p.o., every 12 h for a total of 4 doses)	CYP inhibition and radical scavenging	(79)
Khan *et al*, 2013	Subchronic CCl_4-induced hepatic oxidative stress	Sprague-Dawley male rats	50 mg/kg (p.o., twice weekly)	Antioxidant enzyme restoration and lipid peroxidation reduction	(80)
Küçükler *et al*, 2021	Deltamethrin-induced hepatotoxicity	Male Sprague Dawley rats	25/50 mg/kg (p.o., daily for 30 days)	NF-κB/p38 MAPK inhibition, anti-apoptotic and antioxidative activities	(81)
Khan *et al*, 2012	CCl_4-induced hepatotoxicity	Male Sprague-Dawley rats	50/70 mg/kg (p.o., twice weekly for 4 weeks)	Antioxidation, DNA protection and CYP2E1/p53 restoration	(82)
Zargar *et al*, 2017	TAA-induced hepatotoxicity	Male Wistar rats	10 mg/kg (p.o., daily for 2 weeks)	Antioxidation and DNA protection	(83)
Freitas *et al*, 2022	ABAP-induced hepatic redox imbalance	*In vivo*: Male Swiss mice; *in vitro*: HepG2 cells	*In vivo*: 10 mg/kg (oral, daily for 4 weeks) for chronic study; 10 mg/kg (oral, single dose) for acute study; *in vitro*: 20/40 μg/ml (3 h)	Antioxidation and redox restoration	(84)
Domitrović *et al*, 2012	CCl_4-induced acute hepatotoxicity	Male BALB/ cN mice	10/50/150 mg/kg (i.p., daily for 5 days)	NF-κB suppression, Nrf2/HO-1 induction and antioxidation	(12)
Ali *et al*, 2022	λ-cyhalothrin-induced hepatotoxicity	Male Wistar rats	200 mg/kg (p.o., 5 days/week for 60 days)	Nrf-2 activation and TNF-α suppression	(85)
Wang *et al*, 2024	Zearalenone-induced liver inflammation and injury	Female Kunming mice (6 weeks)	500 mg/kg (diet, 28 days)	NF-κB inhibition and gut barrier protection	(88)
Liu *et al*, 2022	Cadmium-induced liver necroptosis	Isa hens (100 days)	500 mg/kg (diet, 60 days)	Oxidative stress inhibition and MAPK/NF-κB suppression	(89)
Caglayan *et al*, 2019	$HgCl_2$-induced hepatotoxicity	Male Sprague Dawley rats (250-270 g)	50/100 mg/kg (p.o., daily for 7 days)	NF-κB/p38 MAPK signaling inhibition, anti-apoptotic and antioxidative activities	(90)
Naderi *et al*, 2023	PFOA-induced liver injury	Male Wistar rats (200-250 g)	25/50/100 mg/kg (p.o., daily for 4 weeks)	NF-κB/JNK signaling inhibition, antioxidation and anti-apoptotic activity	(19)
Rafiee *et al*, 2023	Paraquat-induced hepatotoxicity	Male Wistar rats	25/50/100 mg/kg (p.o., daily for 14 days)	NF-κB/IL-1β signaling inhibition, antioxidation and anti-apoptotic activity	(91)

Table I. Continued.

B, Drug-induced liver injury

First author, year	Liver disease type	Experimental models	Rutin dose (administration, frequency)	Mechanism	(Refs.)
Anwar and Laila, 2024	Vortioxetine-induced hepatotoxicity	Male Albino rats	25 mg/kg (p.o., daily for 3 weeks)	Caspase-3/cytochrome-C suppression, antioxidation and anti-inflammatory activity	(92)
Erdogan *et al*, 2015	Methotrexate-induced hepatotoxicity	Female Wistar albino rats	100 mg/kg (i.p., daily for 10 days)	Antioxidation and restoration of antioxidant enzymes	(93)
Ahmed *et al*, 2022	Doxorubicin-induced hepatotoxicity	Male Wistar rats (120-145 g)	50 mg/kg (p.o., every other day for 5 weeks)	Nrf2 activation, anti-inflammatory and anti-apoptotic activities	(94)
Nafees *et al*, 2015	Cyclophos-phamide-induced hepatotoxicity	Male Wistar rats (150-200 g)	50/100 mg/kg (p.o., daily for 20 days)	NF-κB/p38 MAPK signaling inhibition, antioxidation and anti-inflammatory activity	(97)
Wu *et al*, 2024	Ensartinib-induced hepatotoxicity	Male C57BL/6J mice (6 weeks)	10 mg/kg (p.o., daily for 4 weeks)	TXNIP inhibition and anti-apoptotic activity	(98)

C, Metabolic dysfunction-associated steatotic liver disease

First author, year	Liver disease type	Experimental models	Rutin dose (administration, frequency)	Mechanism	(Refs.)
Liu *et al*, 2024	Diabetic NAFLD	Male db/db mice (type 2 diabetic model)	100/200 mg/kg (p.o., daily for 8 weeks)	AMPK/SREBP1 signaling activation and inhibition of lipid synthesis, anti-oxidation and anti-inflammatory activity	(102)
Liu *et al*, 2017	NAFLD induced by high-fat diet	Male C57BL/6 mice (8 weeks) fed a high-fat diet (60% fat) for 8 weeks	200 mg/kg (i.p., daily for 4 weeks)	PPARα activation, SREBP1c inhibition, antioxidation and anti-inflammatory activity	(18)
Liang *et al*, 2018	Type 2 diabetes mellitus-associated liver injury	*In vivo*: Male db/db mice (spontaneous T2DM model; 7-8 weeks); *in vitro*: HepG2 liver cells	60/120 mg/kg (p.o., daily for 8 weeks)	IRS-2/PI3K/Akt/GSK-3β pathway activation, AGE inhibition and hepatoprotection	(105)
El-Shial *et al*, 2023	NAFLD induced by high-fructose diet	Male Albino mice (5-weeks) fed 30% fructose in drinking water	50/75/100 mg/kg (p.o., twice weekly for 8 weeks)	CYP2E1/iNOS/JNK1 pathway inhibition and anti-inflammatory activity (validated with isolated rutin)	(106)

Table I. Continued.

C, Metabolic dysfunction-associated steatotic liver disease

First author, year	Liver disease type	Experimental models	Rutin dose (administration, frequency)	Mechanism	(Refs.)
Panchal *et al*, 2011	Non-alcoholic steatohepatitis	Male Wistar rats (8-9 weeks) fed a high-carbohydrate, high-fat diet for 16 weeks	1.6 g/kg diet (8 weeks)	Antioxidation, anti-inflammatory activity and cardioprotection	(107)
Zhang *et al*, 2016	NAFLD	Male ICR mice fed a high-fat diet for 20 weeks	Troxerutin 150 mg/kg (p.o., daily for 20 weeks)	ER stress-mediated NOD/NF-κB axis inhibition and anti-inflammatory activity	(108)
Hawula *et al*, 2021	Genetic iron overload (mirroring type 3 hereditar haemo-chromatosis)	Male *TFR2* knockout mice on a C57BL/6 background	60 mg/kg (p.o., daily for 21 days)	Iron chelation, ferritin reduction and transferrin saturation reduction	(109)

D, Alcoholic liver disease

First author, year	Liver disease type	Experimental models	Rutin dose (administration, frequency)	Mechanism	(Refs.)
Lin *et al*, 2021	AFLD	Male C57BL/6J mice fed a Lieber-DeCarli liquid ethanol diet for 6 weeks	16.4 mg/kg (p.o., daily for 6 weeks)	Antioxidation, reduction of serum lipid levels and suppression of ACC-mediated fatty acid synthesis	(111)
Choi *et al*, 2021	Ethanol-induced hepatotoxicity and hepatic steatosis	Zebrafish larvae (4 dpf) and HepG2 cells	1 μM (*in vitro*: 24 h; *in vivo*: immersion, 24 h)	Inhibition of DRP1-mediated mitochondrial fission and suppression of steatosis	(112)
Wang *et al*, 2022	Ethanol-induced hepatocyte damage	Human hepatic L02 cell line (*in vitro*)	100 μM (*in vitro*, 12 h)	Antioxidation, anti-inflammatory, anti-apoptotic and membrane-protective effects	(113)
Lee *et al*, 2019	Alcoholic liver disease	Human hepatoma cell line HepG2 (*in vitro*)	10/20 μM (pre-treatment for 1 h, then co-treatment with 5% ethanol for 24 h)	Activation of the Nrf2/ARE pathway, antioxidation and anti-inflammatory activity	(115)
Jin *et al*, 2020	Alcoholic liver disease	Female Sprague-Dawley rats with ethanol-induced ALD (40% ethanol; 10 ml/kg for 28 days)	15.65 mg/kg (p.o., daily for 28 days)	Antioxidant enzyme restoration and lipid peroxidation reduction	(117)

Table I. Continued.

E, Other types of liver injury					
First author, year	Liver disease type	Experimental models	Rutin dose (administration, frequency)	Mechanism	(Refs.)
Olmez *et al*, 2023	Liver ischemia/reperfusion-induced distant organ injury	Male Wistar albino rats (255-275 g)	50 mg/kg (p.o., administered 1 h before ischemia induction	Antioxidation, anti-inflammatory activity and inhibition of PMNL infiltration	(121)
Lanteri *et al*, 2007	Hepatic ischemia/reperfusion injury	Male Wistar rats (200-220 g)	30 mg/kg (i.p., daily for 3 days)	Antioxidation, DNA protection and DDAH/NOS signaling modulation	(20)
Pan *et al*, 2014	BDL-induced cholestatic liver injury	Male Sprague-Dawley rats	25 mg/kg (p.o., daily for 4 weeks)	TGF-β/Smad signaling inhibition, anti-inflammatory effects and antioxidation	(123)

p.o., per os; i.p., intraperitoneal; CYP, cytochrome p450; CYP2E1, cytochrome p450 2E1; Nrf2, nuclear factor erythroid 2-related factor 2; NF-κB, nuclear factor-κB; p38 MAPK, p38 mitogen-activated protein kinase; TAA, thioacetamide; ABAP, 2,2'-azobis(2-methylpropionamidine) dihydrochloride; HO-1, heme oxygenase 1; TNF-α, tumor necrosis factor-α; JNK, c-Jun N-terminal kinase; IL-1β, interleukin-1β; TXNIP, thioredoxin-interacting protein; SREBP1, sterol regulatory element-binding protein 1; PPARα, peroxisome proliferator-activated receptor α; IRS-2, insulin receptor substrate 2; AGE, advanced glycation end product; iNOS, inducible nitric oxide synthase; NOD, nucleotide oligomerization domain; ACC, acetyl-coA carboxylase; DRP1, dynamin-related protein 1; ARE, antioxidant response element; PMNL, polymorphonuclear leukocytes; DDAH, dimethylarginine dimethylaminohydrolase; BDL, bile duct ligation; NAFLD, non-alcoholic fatty liver disease AFLD, alcoholic fatty liver disease; PFOA, perfluorooctanoic acid.

nanoparticles. This strategy has effectively enhanced the water solubility and stability of rutin, as well as improved its absorption and utilization efficiency *in vivo* (131). Additionally, encapsulating rutin in chitosan nanoparticles has markedly increased its oral bioavailability and achieved controlled drug release, thereby protecting mitochondrial structures from oxidative stress damage induced by CP (132). In a preclinical study, the rutin-loaded poly(lactic-co-glycolic acid) (PLGA) nanocarrier has demonstrated promising antioxidant and anti-inflammatory activities, demonstrating a notable capacity to modulate antioxidant enzymes and inflammatory response factors. Histopathological analysis has further demonstrated that these nanoparticles inhibit inflammatory cell infiltration, hepatic nodule formation, vascular inflammation and necrosis (73). Furthermore, a previous study has provided evidence that rutin formulations based on the self-nanoemulsifying drug delivery system can enhance its oral bioavailability by ~2.3-fold and that this formulation exhibits potent antioxidant capacity, indicating promising application prospects for improving neurodegenerative diseases (133).

In summary, rutin shows notable potential for treating liver injury, but its clinical application is hindered by markedly low oral bioavailability. However, the advent of nanotechnology has opened new opportunities for the clinical utilization of rutin. Whether through nanoemulsions, coordination polymer nanoparticles, or chitosan and PLGA nanocarriers, nanotechnology can effectively enhance the solubility, stability and absorption efficiency of rutin. This offers more effective and targeted solutions for liver injury treatment, with broad application prospects. It is also important to note that the clinical potential of nanotechnology extends beyond improving the pharmacokinetics of traditional drugs. For example, spherical DNA frameworks, a novel type of nanomaterial, have been shown to specifically accumulate in the liver after intravenous injection without carrying any drugs and efficiently scavenge ROS through their intrinsic structure (134). This structure has demonstrated potent antioxidant and therapeutic effects in a hepatic I/R injury model, highlighting that rationally designed nanomaterials can serve as highly effective targeted therapeutic agents (134). These findings suggest that nanotechnology, whether through modifying existing drugs or creating new nanomedicines, offers broad prospects for achieving more precise and efficient therapeutic effects when employed alongside rutin in liver injury treatment.

Nanodelivery technology provides a novel avenue for the clinical application of rutin. Nevertheless, the clinical translation of treatments using this technology and further exploitation of its application potential are largely constrained by safety and toxicity concerns. With regard to the biosafety of nanocarriers, the liver acts as a primary organ responsible for the enrichment, metabolism and clearance of nanoparticles. Retention and accumulation of nanomaterials within the hepatic tissue tend to provoke oxidative stress and inflammatory damage (135). A relevant study has demonstrated that silver nanoparticles can exert hepatotoxic effects by inducing

mitochondrial fission and excessive generation of ROS, ultimately leading to hepatocyte apoptosis (135). Nanomaterial toxicity is capable of inducing adverse impacts on multiple vital organs and systems covering the liver, lungs, heart, kidneys, brain and immune system. It has also been shown to trigger gastrointestinal disorders exemplified by constipation. Such toxicological concerns markedly hinder the research progress, formulation development and clinical trial promotion of nanoplatforms (136,137). In this context, nanomedicines generally undergo prolonged approval procedures and face stringent market access requirements (138). The systematic assessment of nanomedicine safety and efficacy is necessary throughout the whole preparation manufacturing process (139).

In parallel, rutin nanoformulations possess inherent drawbacks that limit their practical applicability. The preparation of rutin nanoformulations is heavily dependent on sophisticated technological workflows and professional supporting facilities, which result in high production costs and complicated operational procedures (140). Additionally, the physicochemical properties of such formulations are vulnerable to external environmental interference from light exposure, ambient temperature and humidity fluctuations, thereby reducing product shelf life. Rational storage strategies and protective packaging design are therefore required for preserving the bioactivity and therapeutic performance of rutin nanoformulations (140). Current research on rutin nanoformulations still confronts multiple obstacles, including poor aqueous solubility, low bioavailability, rapid metabolism and limited *in vivo* validation, as well as regulatory hurdles and safety concerns (141). Ongoing advances in nanotechnology research are expected to break through these technical and clinical bottlenecks and further facilitate the full realization of the therapeutic value of rutin.

6. Summary and outlook

As a natural flavonoid, rutin holds notable potential in treating various types of liver injury mediated by oxidative stress due to its notable antioxidant pharmacological activity. Studies have provided evidence that rutin has beneficial effects in multiple liver injury models, including chemical-induced liver injury, drug-induced liver injury, metabolism-related liver injury, alcoholic liver disease, hepatic I/R injury and cholestatic liver injury. The core mechanisms of rutin activity involve the regulation of key signaling pathways, such as the Nrf2/ARE, NF-κB and apoptosis pathways, exerting protective effects at multiple levels, including antioxidative and anti-inflammatory effects and the inhibition of hepatocyte apoptosis. However, comparative studies between rutin and clinically used hepatoprotective agents, such as silymarin, bicyclol and N-acetylcysteine, remain insufficient. Therefore, the current evidence does not yet allow a definitive conclusion as to whether rutin is superior to other hepatoprotective drugs (142,143). Nonetheless, owing to its multi-target regulatory properties, natural origin and low toxicity, rutin still exhibits notable potential for drug development. Furthermore, the poor water solubility and low oral bioavailability of rutin markedly limit its clinical translation. Notably, the emergence of nanotechnology has provided new approaches to overcome these challenges. Novel nanoformulations and delivery technologies, such as rutin nanoemulsions and nanoparticles, not only enhance the water solubility and stability of rutin but also notably improve its delivery efficiency and hepatic accumulation, thereby markedly increasing its bioavailability and therapeutic efficacy.

Future research should explore the multiple mechanisms of action of rutin in complex hepatic pathological environments, as well as its synergistic effects with other drugs. Additionally, the innovation and application of rutin nanoformulation technologies are important for improving the targeting capabilities and therapeutic outcomes of rutin treatments. In-depth studies on the safety and biocompatibility of nanomaterials are required, with the evaluation of nanodelivery system safety remaining an important factor in supporting clinical translation. It is expected that. through continued exploration and innovation, rutin and its nanoformulations will provide new breakthroughs in treating oxidative stress-mediated liver injury.

By systematically synthesizing evidence across diverse liver injury models and mechanistic studies, the present review established a unified framework for understanding the hepatoprotective actions of rutin. The present review not only consolidated scattered knowledge but also directly advanced the field of hepatoprotective drug development by pinpointing the Nrf2/NF-κB axis as a central therapeutic target and highlighting nanodelivery as an important translational bottleneck to overcome.

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Authors' contributions

TS was responsible for literature search, study conception and design, analysis and synthesis of the included literature, as well as drafting the initial manuscript. LY provided overarching supervision throughout the project, secured the funding, and was responsible for critically reviewing, revising and editing the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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