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Utilization of Turmeric (*Curcuma longa* L.) as a Hepatoprotector in Patients with NAFLD

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a prevalent liver disorder that can progress from simple steatosis to steatohepatitis and fibrosis. *Curcuma longa* L. and its bioactive compound, curcumin, have been investigated for hepatoprotective effects, but evidence varies across bioinformatics, in vitro, animal, and human studies. This systematic review aimed to synthesize evidence on the hepatoprotective effects and molecular mechanisms of *Curcuma longa* and curcumin in NAFLD, distinguishing preclinical from clinical evidence. Literature searches were conducted in PubMed, Europe PMC, and Google Scholar using terms related to *Curcuma longa*, curcumin, hepatoprotection, inflammation, and NAFLD, following PRISMA 2020 principles. Evidence suggests curcumin may reduce hepatic lipid accumulation and modulate oxidative stress, inflammation, insulin sensitivity, and gut–liver pathways. However, clinical evidence remains limited, with differences in formulations, doses, durations, and outcomes. Curcumin is therefore a promising investigational adjunct, but standardized clinical trials are needed to establish efficacy, optimal dosing, formulation, and long-term safety.

Keywords : Anti-inflammatory; Curcuma longa L; Curcumin; hepatoprotective ; NAFLD

INTRODUCTION

The liver is a primary metabolic organ responsible for the metabolism of carbohydrates, proteins, and lipids, the detoxification of drugs and toxins, and bile production. Liver dysfunction can have far-reaching effects on the body's metabolic balance. NAFLD has emerged as a serious global health issue, with prevalence rates rising alongside the increasing incidence of obesity and metabolic syndrome (Yin, Guo and Liu, 2023; He *et al.*, 2024a). Globally, the prevalence of NAFLD is estimated to reach 25% to 30% of the adult population. In the Asian region, the prevalence of this disease is recorded at approximately 29.62% and shows a continuing upward trend. In fact, in some countries such as Canada, NAFLD is projected to become the leading cause of cirrhosis diagnoses by 2040, while in the United States, the disease already affects approximately 30% of the population and has the potential to become the leading cause of liver transplants (Lamichhane, D. Y. Lee, *et al.*, 2024; Fadlallah *et al.*, 2025). Despite its very high prevalence, to date, there is no specific pharmacological drug approved by the FDA to directly treat NAFLD (Mahmoudi *et al.*, 2022) .

The progression of NAFLD begins with the accumulation of ectopic fat in the liver, defined as the presence of steatosis in more than 5% of liver cells in the absence of excessive alcohol consumption (Fu *et al.*, 2022; Yin *et al.*, 2023). Based on the "multiple-hit hypothesis," the development of this disease is triggered by various factors acting concurrently, including insulin resistance, oxidative stress, inflammation, and gut microbiota imbalance (Teng *et al.*,

2022). The stages of this disease progress from simple steatosis (NAFL) to non-alcoholic steatohepatitis (NASH), which involves liver cell damage and inflammation (Filipovic, Lukic, Mijac, Marjanovic-haljilji, *et al.*, 2021; Yin *et al.*, 2023). If left untreated, this condition can progress to fibrosis, liver cirrhosis, and even hepatocellular carcinoma (HCC) (Teng *et al.*, 2022).

With the growing interest in natural product-based therapies, various medicinal plants are being investigated as sources of hepatoprotective compounds. Hepatoprotective agents are compounds capable of preventing or mitigating liver cell damage caused by oxidative stress, inflammation, toxins, or metabolic disorders. Turmeric (*Curcuma longa* L.) contains curcumin as its primary active compound; curcumin exhibits antioxidant and anti-inflammatory activities and has the potential to inhibit the process of liver fibrosis. Although various preclinical studies have demonstrated the hepatoprotective effects of curcumin, clinical evidence regarding its potential role in patients with NAFLD remains limited and requires systematic evaluation.. Therefore, this literature review was conducted to analyze the potential of Curcuma longa L. as a hepatoprotective agent for NAFLD (Utami, Novianry and Zakiah, 2021).

Curcumin possesses various pharmacological activities including antioxidant, anti-inflammatory, anti-lipogenic, and antifibrotic properties that are theoretically relevant to the various pathological processes involved in NAFLD.Experimental studies demonstrate that curcumin can reduce lipid accumulation in liver cells and modulate pathways involved in lipid metabolism. In hepatocyte models exhibiting lipid accumulation, curcumin enhances the phosphorylation of AMP-activated protein kinase (AMPK) and suppresses the expression of sterol regulatory element-binding protein-1 (SREBP-1) and fatty acid synthase (FAS), thereby inhibiting hepatic lipogenesis. Curcumin also upregulates the expression of peroxisome proliferator-activated receptor-α (PPAR-α), which plays a role in fatty acid oxidation. These mechanisms indicate that curcumin has the potential to reduce triglyceride accumulation in hepatocytes by balancing decreased lipid synthesis with increased fatty acid oxidation (Mao *et al.*, 2021; Zeng *et al.*, 2022).

The hepatoprotective effects of curcumin are closely associated with its ability to regulate inflammatory responses. Oxidative stress and hepatocellular injury can activate nuclear factor kappa B (NF-κB) and various inflammatory mediators, thereby exacerbating liver tissue damage. Curcumin has been reported to inhibit NF-κB activation and suppress the production of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). In addition to NF-κB, preclinical evidence suggests that curcumin can modulate the NLRP3 inflammasome, a protein complex involved in inflammatory responses and the release of IL-1β and IL-18. Modulation of these inflammatory pathways provides a biological basis for the potential of curcumin to reduce the pro-inflammatory environment that contributes to the progression of hepatocellular injury in non-alcoholic fatty liver disease (NAFLD). (Kang *et al.*, 2013; Malik and Mrcp, 2024a; Liu, Zheng and Wang, 2026).

Several relevant studies from the past five years reinforce these findings; notably, a 2024 randomized controlled trial demonstrated that 24 weeks of curcumin supplementation significantly reduced liver fat content (CAP values) and improved gut microbiota in patients with NAFLD in China (He *et al.*, 2024b). A 2024 study using a model of aged female mice found that a curcumin-rich diet could mitigate NAFLD by improving insulin sensitivity and reducing triglyceride and cholesterol deposition in the liver (Lamichhane, D. Lee, *et al.*, 2024). A 2022 bioinformatics analysis identified 14 specific protein targets with which curcumin interacts to inhibit NAFLD progression, including targets involved in the steatosis and fibrosis stages (Mahmoudi *et al.*, 2022). Furthermore, a 2022 experimental study validated that curcumin derivatives (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) all possess

hepatoprotective effects by suppressing lipid accumulation induced by a methionine-choline-deficient diet (Lee *et al.*, 2022; Genua and Cusi, 2024).

Research gap and rationale. Previous reviews and meta-analyses have primarily summarized clinical trial outcomes of curcumin in NAFLD, such as liver enzymes, anthropometric measures, and metabolic parameters. In contrast, the present review was undertaken to address a broader translational gap: the available evidence is dispersed across bioinformatics, cellular experiments, animal models, and human studies, yet these evidence types have often been discussed without sufficient distinction in their level of inference. A systematic synthesis that explicitly separates mechanistic preclinical evidence from human clinical evidence is needed to clarify which proposed pathways are biologically plausible, which findings have been observed in patients, and where translation from mechanism to clinically meaningful outcomes remains uncertain. This review therefore adds value by organizing the evidence according to study design, population or model, intervention, outcome domain, and evidentiary strength rather than presenting all findings as equivalent support for therapeutic efficacy.

METHODS

This study was designed as a systematic review and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement. PRISMA 2020 was used to improve transparency and reproducibility in the identification, screening, eligibility assessment, and reporting of included studies. The review question focused on the hepatoprotective effects of Curcuma longa L. and curcumin in NAFLD and on the molecular pathways proposed to underlie these effects.

A systematic literature search was performed in PubMed, Europe PMC, and Google Scholar. The search strategy combined controlled and free-text terms related to the intervention and condition, including: “Curcuma longa”, “turmeric”, “curcumin”, “hepatoprotective”, “liver injury”, “anti-inflammatory”, “oxidative stress”, “NAFLD”, “non-alcoholic fatty liver disease”, and “metabolic dysfunction-associated steatotic liver disease”. Boolean operators were used to combine concepts, with the core strategy structured as: (“Curcuma longa” OR turmeric OR curcumin) AND (“NAFLD” OR “non-alcoholic fatty liver disease” OR MASLD) AND (hepatoprotective OR inflammation OR “oxidative stress” OR steatosis). The literature search was conducted in August 2026. Publications from January 2021 to August 2026 were prioritized, while earlier landmark studies were considered when necessary to provide mechanistic background when required to explain established molecular mechanisms. The final search was completed using the databases and search records reported in the manuscript.

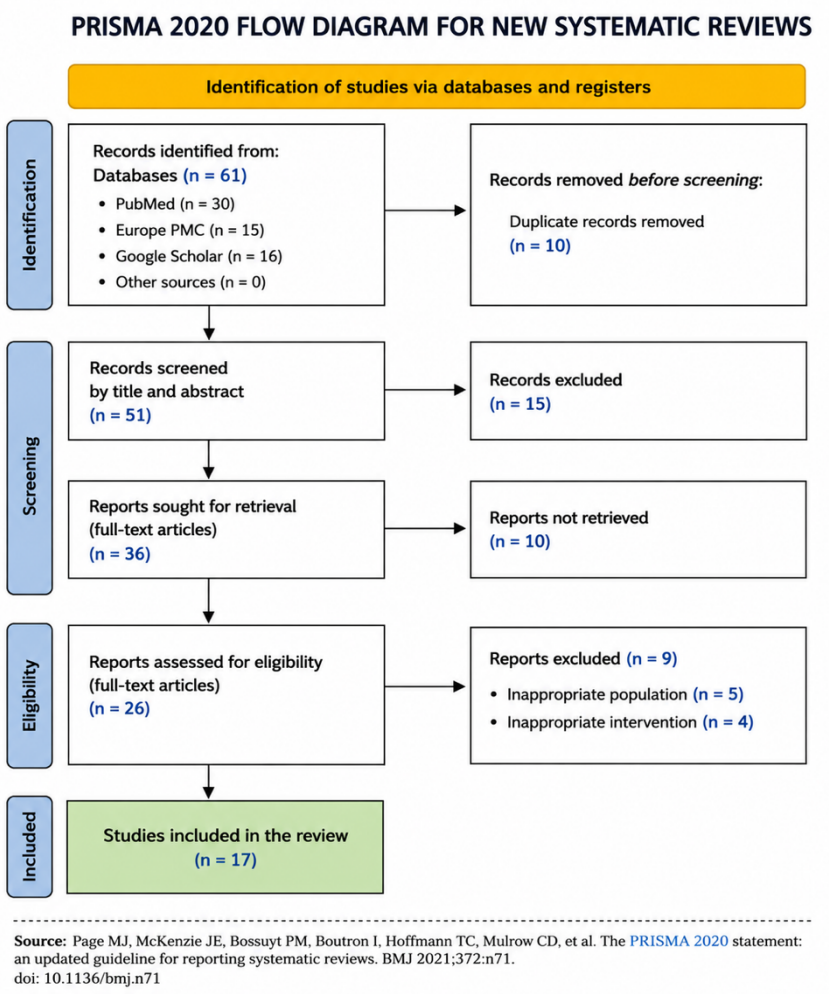
Studies were eligible when they: (1) evaluated Curcuma longa, curcumin, or defined curcuminoid preparations; (2) investigated NAFLD/MASLD or NAFLD-relevant hepatic steatosis, liver injury, inflammation, oxidative stress, insulin resistance, or fibrosis; (3) used bioinformatics, in vitro, animal, or human clinical designs; and (4) reported outcomes relevant to hepatoprotection or NAFLD pathobiology. Reviews, editorials, conference abstracts without sufficient methodological information, duplicate records, studies unrelated to curcumin/Curcuma longa, and studies in which the liver model was not relevant to the review question were excluded. Studies of general hepatotoxicity were not used as direct clinical evidence for NAFLD and were interpreted separately as indirect mechanistic evidence.

Records were exported and duplicates removed. Titles and abstracts were screened against the eligibility criteria, followed by full-text assessment of potentially relevant reports. As reported in the PRISMA flow process, 61 records were identified, 10 duplicates were removed, 51 records were screened, 36 full texts were sought, 10 reports were not retrieved,

and 17 articles were included in the final review. Data were extracted into a structured evidence table containing study design, number and type of studies, population or experimental model, intervention and comparator where applicable, primary outcomes, principal findings, and level of evidence. Because of substantial heterogeneity in study designs, experimental models, formulations, doses, durations, and outcome measures, meta-analysis was not performed and findings were synthesized narratively and stratified by evidence level.

Given the broad inclusion of bioinformatics, in vitro, animal, and human studies, a single validated risk-of-bias instrument could not be applied consistently across all evidence types. Accordingly, the review did not pool methodological quality scores, and the level of inference was instead interpreted primarily according to study design and directness of relevance to NAFLD. This limitation should be considered when interpreting the overall conclusions.

The literature screening process followed the PRISMA 2020 framework. The initial search identified 61 records, comprising 30 records from PubMed, 15 from Europe PMC, and 16 from Google Scholar. After removal of 10 duplicates, 51 records underwent title and abstract screening. Fifteen records were excluded at this stage, and 36 reports were sought for full-text retrieval. Ten reports could not be retrieved, leaving 26 full-text reports assessed for eligibility. Seventeen studies met the eligibility criteria and were included in the final synthesis. Because detailed reasons for each full-text exclusion were not consistently available in the screening record, this should be acknowledged as a reporting limitation and the PRISMA flow diagram should reflect the documented screening numbers.



RESULTS

The final review included 17 eligible studies spanning bioinformatics, in vitro, animal, and human clinical evidence. The evidence base was heterogeneous and was therefore synthesized by study design and level of inference rather than treated as a single body of equivalent evidence. Bioinformatics evidence identified candidate molecular targets and pathways potentially linking curcumin with lipid metabolism, oxidative stress, and inflammatory signaling, but these findings remain hypothesis-generating. In vitro and animal studies provided the main mechanistic evidence, consistently reporting reductions in hepatic or intracellular lipid accumulation and modulation of AMPK-related lipogenesis, NF-κB/TLR-related inflammation, antioxidant defenses, and selected insulin-signaling pathways. Animal evidence also suggested potential effects on gut–liver signaling and hepatic metabolic regulation, although differences in induction models, doses, formulations, and treatment durations limit direct translation to patients.

Human evidence was comparatively limited. The included randomized clinical evidence reported improvements in selected liver fat and metabolic outcomes, including reduced CAP values and changes in triglyceride and glucose parameters. However, clinical studies differed in formulation, dose, duration, and outcome measurement, and most did not establish histological improvement, fibrosis regression, or long-term clinical benefit. Overall, the direction of evidence supports biological plausibility for hepatoprotective effects of curcumin in NAFLD, but the certainty of clinical conclusions is lower than the consistency of preclinical mechanistic findings.

Table 1. Systematic synthesis of evidence by study design and level of evidence

Evidence level / design	No. of included studies*	Population/ model	Intervention	Main outcomes	Interpretation
Bioinformatics	1	NAFLD-related molecular datasets	Curcumin target mapping	14 candidate protein targets; lipid and oxidative-stress pathways	Hypothesis-generating; requires experimental and clinical validation
In vitro / mechanistic	At least 1 primary study	Oleic-acid-induced HepG2 and related cellular models	Curcumin/curcuminoids	↓ intracellular lipid accumulation; AMPK activation; ↓ lipogenic signaling	Mechanistic plausibility; not direct clinical evidence
Animal NAFLD/metabolic models	Multiple primary studies	Diet-induced or nutritionally stressed rodents	Curcumin-rich diet or curcumin preparations	↓ hepatic TG/cholesterol; improved insulin-related signaling and steatosis markers	Supportive preclinical evidence; translation limited by model heterogeneity
Animal indirect	Multiple primary studies	Rodent hepatotoxicit	Curcumin or Cur-NLC	↑ antioxidant defenses; ↓ inflammatory/apo	Indirect support for hepatoprotection

liver-injury models		y/inflammation models		ptotic markers; improved liver enzymes	; not NAFLD-specific clinical evidence
Human randomized clinical evidence	Limited	Adults with NAFLD	Curcumin supplementation	Improvement in selected liver-fat and metabolic outcomes, including CAP in one trial	Most clinically relevant evidence, but limited by sample size, duration, and formulation heterogeneity

DISCUSSION

The Use of Turmeric (Curcuma longa L.) as a Hepatoprotector

Research in the literature consistently demonstrates that turmeric through its primary active compound, curcumin plays a crucial role as a hepatoprotective agent for individuals with NAFLD. Various studies have explored the use of curcumin in diverse forms, ranging from crude extracts and single compounds to nanotechnology-based formulations. An in vivo study on rats demonstrated that the combination of Curcuma domestica and Tithonia diversifolia extracts did not cause significant changes in overall SGOT and SGPT parameters, thereby indicating hepatic safety under the experimental conditions used. However, this study could not conclusively demonstrate a specific hepatoprotective effect of turmeric due to the use of a combined extract, the relatively small number of animals per group, the DMBA-induced cancer model, and the absence of molecular biomarkers or liver histopathology data (Anugerah, Pratiwi and Wahyuningsih, 2018; Mahmoudi *et al.*, 2022).

Curcumin exhibits hepatoprotective potential through the modulation of pathways involving antioxidants, lipid metabolism, inflammation, insulin resistance, and fibrosis. Bioinformatics evidence identifies NFE2L2/NRF2, PPARA, IL1A, TGFB1, PRKCE, GSTA1, and GSTP1 as potential targets linking curcumin to the pathogenesis of NAFLD. However, most of these associations remain predictive and require experimental validation (Lee *et al.*, 2022; Mahmoudi *et al.*, 2022). The primary mechanism involves the activation of the AMPK (adenosine monophosphate-activated protein kinase) pathway, which subsequently inhibits the expression of genes encoding for fat-related proteins such as SREBP-1c, FAS (fatty acid synthase), and PPAR-γ (Lee *et al.*, 2022).

Molecular-Level Repair of Damage

In addition to reducing fat, curcumin repairs liver cell damage caused by oxidative stress and inflammation. Studies indicate that curcumin can suppress the NF-κB pathway and pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6. At the antioxidant level, curcumin increases levels of GSH, SOD, and catalase, while suppressing damage markers such as malondialdehyde (MDA). This study is significant because it comprehensively explains the hepatoprotective mechanism of Cur-NLC through its anti-inflammatory, antioxidant, and anti-apoptotic activities. This is evidenced by a decrease in the expression of NF-κB, TNF-α, IL-1β, IL-6, and MDA, accompanied by an increase in GSH, SOD, and catalase levels. In addition to measuring ALT and AST, this study also analyzed apoptosis-related proteins (Bax, Caspase-3, Apaf-1) and the oxidative stress marker 4-HNE, thereby providing stronger mechanistic evidence. However, this study still has limitations because it used a Wistar rat model with

cypermethrin induction and a study duration of only 15 days; therefore, the results cannot yet be generalized to humans or other types of liver damage without further research. Curcumin demonstrates potential in ameliorating liver damage through antioxidant, anti-inflammatory, and anti-apoptotic mechanisms.

Meta-analyses of randomized controlled trials (RCTs) involving patients with non-alcoholic fatty liver disease (NAFLD) show reductions in ALT and AST levels, providing clinical support for curcumin's ability to improve markers of hepatocellular injury. However, significant study heterogeneity stemming from variations in dosage, duration, sample size, study populations, and curcumin formulations limits the strength of these conclusions. Meanwhile, studies on Cur-NLC (curcumin-loaded nanostructured lipid carriers) in rats provide more comprehensive molecular evidence, demonstrating reduced lipid peroxidation; increased levels of GSH, SOD, and catalase; and downregulated NF-κB, pro-inflammatory cytokines, and apoptotic pathways, alongside improvements in liver histopathology. The advantage of nano-lipid formulations lies in their potential to enhance curcumin's inherently low bioavailability. Nevertheless, these studies utilized small animal samples (n=6 per group) and a cypermethrin-induced hepatotoxicity model, meaning the findings cannot yet be directly generalized to NAFLD patients. Thus, while curcumin shows great promise as a hepatoprotective agent, further RCTs are required—featuring larger sample sizes, standardized formulations, longer durations, and assessments of pharmacokinetics and molecular biomarkers to establish the relationship between bioavailability, molecular targets, and clinical benefits (Hussain *et al.*, 2023; Ebrahimzadeh *et al.*, 2025).

Curcumin Inhibits Fat Formation (Lipogenesis)

Curcumin inhibits fat formation and enhances fatty acid breakdown (β-oxidation). Curcumin inhibits hepatic fat accumulation by activating AMP-Activated Protein Kinase (AMPK), a key regulator of energy metabolism; suppressing the expression of Sterol Regulatory Element-Binding Protein-1c (SREBP-1c), a transcription factor that regulates fatty acid synthesis; inhibiting lipogenic enzymes such as Fatty Acid Synthase (FAS) and Acetyl-CoA Carboxylase (ACC); and increasing the activity of Peroxisome Proliferator-Activated Receptor-α (PPAR-α), thereby enhancing fatty acid oxidation. Consequently, triglyceride levels in hepatocytes are reduced. Curcumin inhibits fat formation in the liver (lipogenesis). Curcumin has the potential to inhibit hepatic fat accumulation, primarily by modulating lipid and triglyceride metabolism; bioinformatic analyses indicate the involvement of targets such as PPARA, LDLR, PRKCD, LEP, and NFE2L2 in lipid metabolism pathways and NAFLD, suggesting a theoretical capacity to suppress lipogenesis and support hepatocyte lipid homeostasis—notably, PRKCD dysfunction is linked to the accumulation of triglycerides and lipid droplets. Bioinformatics research has mapped these molecular mechanisms extensively, identifying 14 potential targets for curcumin, while meta-analyses provide clinical support from human data; involving 16 studies and 975 patients, these analyses demonstrated a reduction in total glycerides (by approximately 13.22 units) and waist circumference, suggesting a decrease in the lipid or metabolic burden contributing to steatosis. However, limitations remain: bioinformatic studies are predictive and have not yet proven that these targets directly cause a reduction in hepatocyte fat, whereas meta-analyses did not directly measure intrahepatic fat content or hepatocyte lipogenesis, and results across studies were influenced by small sample sizes, short durations, variations in curcumin dosage and formulation, and limited data regarding the content and dosage of the agents used (Malik and Mrcp, 2024b).

Curcumin Improves Insulin Sensitivity

Specifically by increasing insulin receptor phosphorylation and GLUT4 translocation, as well as by activating AMPK—thereby lowering blood glucose levels. Consequently, hepatic glucose production decreases, fatty acid influx into the liver is reduced, and triglyceride formation is diminished (Yan *et al.*, 2020).

Curcumin has the potential to improve insulin sensitivity while reducing hepatic steatosis, primarily through mechanisms involving the gut-liver axis. A study by (R. Li *et al.*, 2021) on C57BL/6 mice fed a high-fat diet for 10 weeks demonstrated that 0.2% curcumin reduced hepatic steatosis and enhanced insulin sensitivity; these changes were accompanied by decreased LPS/endotoxin levels, improved microbiota composition, and increased short-chain fatty acid (SCFA) levels. Administration of curcumin at 100 mg/kg/day for 4 weeks increased Akt phosphorylation following insulin stimulation, suppressed gluconeogenesis (Pck1, G6pc) and de novo lipogenesis (Srebf1, Fasn, Acaca, Scd1), and reduced hepatic triglycerides; these effects were abolished upon gut microbiota depletion but could be restored via fecal microbiota transplantation, with FGF15 identified as a putative mediator (Zhong *et al.*, 2022). As both studies utilized animal models, the findings cannot yet be directly generalized to patients with NAFLD; furthermore, given curcumin's very low systemic bioavailability, the relative contribution of curcumin acting directly within liver tissue versus effects mediated by the microbiota requires further clarification (S. Li *et al.*, 2021; Zhong *et al.*, 2022).

Curcumin Suppresses Inflammation

Inhibiting Nuclear Factor-kappa B (NF-κB) and Toll-like receptor 4 (TLR4). Consequently, the production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and MCP-1) decreases. This reduction in pro-inflammatory cytokines leads to decreased inflammatory cell infiltration and reduced hepatocyte damage (Ngu *et al.*, 2022). This original experimental study involved 50 KM mice divided into five groups. A liver injury model was induced using LPS and D-galactosamine, followed by treatment with curcumin (100 mg/kg), paeoniflorin, or a combination of both for 14 days. The paeoniflorin–curcumin combination ameliorated histopathological damage and hepatocyte ultrastructural alterations, increased levels of SOD, GSH-Px, and CAT, and reduced inflammatory cytokines such as IFN-γ, TNF-α, and IL-1. At the molecular level, the treatment downregulated the expression of TLR4, MyD88, IκBα, and NLRP3, thereby supporting the inhibition of the TLR4 → MyD88 → NF-κB → NLRP3 → proinflammatory cytokine pathway. Curcumin—particularly in combination with paeoniflorin—has the potential to suppress inflammation and alleviate liver injury by inhibiting TLR4/NF-κB/NLRP3 activation; however, this study cannot specifically attribute the observed effects solely to curcumin, as the intervention involved a combination of two compounds (Wu *et al.*, 2025).

Curcumin Inhibits Liver Fibrosis.

Prolonged inflammation and metabolic disturbances in NAFLD can promote the development of liver fibrosis. One important mechanism involves the activation of hepatic stellate cells (HSCs), which produce excessive extracellular matrix and collagen, leading to the formation of liver scar tissue. Curcumin may inhibit this process by suppressing HSC activation and regulating the transforming growth factor-β1 (TGF-β1)/Smad signaling pathway. Curcumin has been reported to reduce the expression of TGF-β1 and Smad2/3, thereby decreasing the synthesis of type I and III collagen. Through these mechanisms, curcumin may reduce liver scar formation and potentially slow the progression of fibrosis toward cirrhosis (Li et al., 2025).

Clinical studies in patients with NAFLD are still limited. Many studies have relatively small sample sizes and short intervention periods. In addition, substantial differences exist in curcumin dosage, formulation, and treatment duration. The use of conventional curcumin, curcumin combined with bioavailability enhancers, and nano-curcumin may produce different biological effects, making direct comparisons between studies difficult (Hernández-aquino *et al.*, 2020)

Curcumin Improves Mitochondrial Function.

Mitochondrial dysfunction occurs in MASLD. Curcumin enhances mitochondrial biogenesis via PGC-1α, increases ATP production, and reduces mitochondrial ROS formation. Consequently, lipid metabolism becomes more efficient (Malik and Mrcp, 2024a). Curcumin may improve mitochondrial function by promoting mitochondrial biogenesis through the activation of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α). Increased PGC-1α activity may subsequently regulate mitochondrial biogenesis and energy metabolism, improving ATP production and fatty acid utilization. Curcumin may also reduce mitochondrial ROS and oxidative damage, thereby helping to maintain mitochondrial function and limiting inflammation and lipid peroxidation (Zheng *et al.*, 2023; Kim *et al.*, 2024).

Through these mechanisms, curcumin may interrupt the cycle of mitochondrial dysfunction, oxidative stress, and hepatic lipid accumulation in NAFLD/MASLD. However, most evidence remains derived from experimental studies, and further well-designed clinical trials are needed to confirm these mitochondrial benefits in humans (Zheng *et al.*, 2023; Kim *et al.*, 2024)

Curcumin Improves Gut Microbiota Composition

Increasing beneficial bacteria, reducing pathogenic bacteria, and strengthening intestinal barrier integrity. This reduces endotoxin (LPS) translocation to the liver, thereby diminishing inflammation via the TLR4 pathway (Li et al., 2025). Gut dysbiosis contributes to NAFLD progression by impairing intestinal barrier integrity and increasing the translocation of lipopolysaccharide (LPS) into the portal circulation. Curcumin may improve gut microbiota composition by increasing beneficial bacteria, including *Bacteroides*, while reducing endotoxin-producing bacteria. Curcumin can also strengthen intestinal barrier integrity by increasing tight-junction proteins such as ZO-1 and occluding . Consequently, reduced intestinal permeability may limit LPS translocation to the liver and suppress LPS-mediated activation of the TLR4/NF-κB inflammatory pathway, thereby reducing hepatic inflammation and steatosis (Zheng *et al.*, 2023).

An important advantage of curcumin is its potential to simultaneously regulate the gut microbiota, intestinal barrier, inflammation, and lipid metabolism. However, evidence remains limited by differences in curcumin formulations, doses, individual microbiota composition, and study populations. Most mechanistic evidence is also derived from animal studies, although a recent randomized controlled trial in patients demonstrated that curcumin supplementation was associated with reduced hepatic fat and alterations in gut microbiota-dependent bile acid metabolism. Therefore, further large-scale clinical studies are required to confirm its microbiota-mediated benefits in NAFLD (Zheng *et al.*, 2023).

Current evidence indicates that curcumin has potential hepatoprotective activity relevant to NAFLD, but the strength of support differs substantially across preclinical and human studies.

Table 2. Evaluation Results of Curcumin Hepatoprotective Activity in NAFLD

Mechanism	Molecular Target	Effect
Reduces lipogenesis	AMPK ↑, SREBP-1c ↓, FAS ↓, ACC ↓	Liver fat decreases
Increasing β-oxidation	PPAR-α ↑	Fat burning increases.
Antioxidants	Nrf2 ↑, SOD ↑, CAT ↑, GPx ↑	ROS declined.
Anti-inflammatory	NF-κB ↓, TNF-α ↓, IL-6 ↓	Inflammation decreases
Antifibrotic	TGF-β1 ↓, Smad ↓	Fibrosis is reduced.
Antiapoptotic	Bcl-2 ↑, Bax ↓, Caspase-3 ↓	Hepatocytes are protected.
Insulin sensitivity	AMPK ↑, GLUT4 ↑	Insulin resistance decreases.
Microbiota modulation	TLR4/LPS ↓	Liver inflammation decreases.

Research Gap and Contribution of the Present Systematic Review

Based on the literature analyzed, there are several points of novelty that differentiate the latest research from previous classic studies:

a. Focus on Geriatric and Sex-Specific Models: A recent study (2024) highlights the effects of curcumin on aged female mice, providing new data on curcumin's efficacy in the context of aging and nutritional stress specific to females (Lamichhane, D. Lee, *et al.*, 2024).
b. Modulation of Gut Microbiota and Bile Acids: Recent research has shifted from focusing solely on liver cells to the interactions of the gut-liver axis. It has been found that curcumin acts through the modulation of gut microbiota and bile acid metabolism, a process dependent on the activation of the TGR5 receptor (He *et al.*, 2024b).
c. Comparative Analysis of Curcumin Derivatives: A 2022 study offers new insights by comparing three major derivatives: curcumin (CM), demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC). The results indicate that BDMC and CM often exhibit stronger inhibitory effects on lipogenesis compared to DMC (Lee *et al.*, 2022).
d. Multi-compound Synergy: Novelty is also evident in the exploration of synergy between curcumin and other compounds such as resveratrol, where the combination of the two has proven more effective through the modulation of the PI3K/AKT/mTOR and HIF-1/VEGF pathways (He *et al.*, 2023).

Pharmacological Effects

In the field of pharmacology, Non-Alcoholic Fatty Liver Disease (NAFLD)—currently also known as Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD)—is a chronic liver disease with a globally rising prevalence, driven by the increasing incidence

of obesity, type 2 diabetes mellitus, and metabolic syndrome. This condition has emerged as a leading cause of chronic liver disease in many countries, surpassing the prevalence of liver diseases caused by viral infections or alcohol consumption. (Fadlallah et al., 2025b). The pathogenesis of NAFLD is multifactorial and is explained by the "multiple-hit" concept, involving the interaction of various metabolic, genetic, and nutritional factors, oxidative stress, and alterations in gut microbiota composition, which collectively trigger fat accumulation, inflammation, and hepatocyte damage (Teng *et al.*, 2022). At the molecular level, increased accumulation of free fatty acids within hepatocytes causes lipotoxicity, triggering endoplasmic reticulum stress, mitochondrial dysfunction, and increased formation of reactive oxygen species (ROS). These conditions subsequently activate hepatic stellate cells, leading to extracellular matrix deposition that contributes to the development of fibrosis in NAFLD patients (Filipovic, Lukic, Mijac, Marjanovic-Haljilji, *et al.*, 2021; Yin *et al.*, 2023).

Establishing a diagnosis of NAFLD requires an approach capable of accurately identifying steatosis, inflammation, and the degree of liver fibrosis. Although liver biopsy remains the gold standard for assessing histopathological changes, the procedure has several limitations such as its invasive nature, the risk of complications, and the potential for sampling error which restrict its use in clinical practice (Fu *et al.*, 2022). Therefore, various non-invasive diagnostic methods continue to be developed to enhance the effectiveness of early detection. One imaging modality with high sensitivity is Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF), which is capable of quantitatively measuring liver fat content with good reproducibility.(Yin et al., 2023c). In addition to imaging, various serum biomarkers such as the Fatty Liver Index (FLI) and the Fibrosis-4 (FIB-4) score are widely used for initial screening; they are more accessible, cost-effective, and reasonably accurate in identifying patients at risk of liver fibrosis. Early detection of fibrosis is crucial, as the progression of fibrosis is a primary determinant of clinical outcomes and long-term prognosis in patients with NAFLD (Yin *et al.*, 2023).

To date, lifestyle modification remains the primary therapeutic approach for NAFLD. Weight loss achieved through a combination of dietary changes and increased physical activity has been shown to reduce hepatic fat accumulation, improve insulin sensitivity, and decrease the severity of inflammation. Various studies indicate that a weight loss of 7–10% is associated with significant histological improvement, including the resolution of non-alcoholic steatohepatitis (NASH) and a reduction in the severity of fibrosis (Yin *et al.*, 2023). Among the various recommended dietary patterns, the Mediterranean diet stands out as one of the most strongly supported approaches, as it is rich in unsaturated fatty acids, fiber, antioxidants, and bioactive compounds capable of improving insulin sensitivity while modulating the balance of the gut microbiota (Filipovic, Lukic, Mijac, Marjanovic-Haljilji, *et al.*, 2021).

Although no pharmacological therapy has yet been specifically approved for the treatment of NAFLD/NASH, various drug candidates are currently being evaluated in Phase II and III clinical trials with promising results (Yin *et al.*, 2023). Current therapeutic management of NAFLD, now termed metabolic dysfunction-associated steatotic liver disease (MASLD), primarily emphasizes lifestyle modification, including weight loss, dietary improvement, and physical activity, together with the management of associated metabolic comorbidities. For patients with more advanced disease, pharmacological approaches are being evaluated or used according to specific indications and disease stages, with evidence for liver-specific benefits varying among therapeutic agents. Curcumin has shown potential hepatoprotective effects in experimental models and small clinical studies of NAFLD/MASLD, including improvements in hepatic steatosis, liver

enzyme levels, oxidative stress, and inflammatory pathways. However, the available clinical evidence remains limited and heterogeneous, and there is currently insufficient evidence to establish curcumin as an effective liver-directed therapy for NAFLD/MASLD. Therefore, curcumin should not be considered a replacement for established lifestyle and clinically indicated therapeutic approaches but rather a potential adjunctive strategy requiring further validation in well-designed clinical trials using liver-specific outcomes, including hepatic steatosis, inflammation, and fibrosis (Zheng *et al.*, 2023)

Research indicates that the gut-liver axis plays a crucial role in the pathogenesis of NAFLD, making it a potential therapeutic target. Gut microbiota imbalance (dysbiosis) can increase intestinal permeability ("leaky gut"), allowing bacterial endotoxins such as lipopolysaccharides (LPS) to more easily enter the portal circulation and trigger an inflammatory response in the liver. The gut–liver axis represents another relevant therapeutic pathway in NAFLD. Dysbiosis and increased intestinal permeability may enhance lipopolysaccharide translocation and promote hepatic inflammatory responses. In this context, the reported ability of curcumin to modulate gut microbiota and attenuate LPS/TLR4-related inflammatory signaling provides a potential mechanistic link between curcumin and the gut–liver axis in NAFLD. Nevertheless, the clinical significance of this mechanism requires further investigation (Fu *et al.*, 2022).

Overall, the hepatoprotective potential of curcumin in NAFLD appears to involve multiple interconnected mechanisms, including modulation of hepatic lipid metabolism, attenuation of oxidative stress and inflammatory signaling, improvement of insulin sensitivity, and regulation of fibrogenic pathways. However, the strength of evidence supporting these mechanisms varies across bioinformatic, in vitro, animal, and human studies. Therefore, these mechanistic findings should be interpreted according to the level of evidence from which they were derived.n The available evidence supports several biologically plausible hepatoprotective mechanisms of curcumin in NAFLD; however, these findings should be interpreted cautiously because the strength and clinical relevance of the evidence vary considerably across studies. A substantial proportion of the mechanistic evidence is derived from bioinformatic, in vitro, and animal studies. These studies are valuable for identifying potential molecular targets involved in hepatic lipid accumulation, oxidative stress, inflammation, and fibrogenesis, but their findings cannot be directly extrapolated to clinical efficacy in patients with NAFLD (Jarhahzadeh *et al.*, 2021).

The available randomized controlled trials included in this review have specifically evaluated turmeric or curcumin preparations in patients with NAFLD and reported changes in liver-related outcomes, such as liver enzymes, hepatic steatosis or liver echogenicity, as well as selected metabolic and inflammatory parameters. However, the clinical evidence remains limited because most trials involved relatively modest sample sizes and short intervention periods. Therefore, improvements in biochemical or imaging-based parameters should not automatically be interpreted as evidence of histological improvement or reversal of liver (Jarhahzadeh *et al.*, 2021)(Safari, Bagherniya and Khoram, 2023)

Another important limitation is the substantial heterogeneity of the curcumin interventions evaluated in NAFLD-specific clinical studies. investigated turmeric at 2 g/day for eight weeks, whereas Hosseinian et al. (2022) evaluated phytosomal curcuminoids at 250 mg/day for two months, and Beheshti Namdar et al. (2023) investigated nano-micelle curcumin at 160 mg/day for 60 days. Differences in formulation, dose, treatment duration, and liver-related outcomes limit direct comparisons among

studies. Consequently, beneficial findings observed with one preparation should not automatically be generalized to other turmeric or curcumin formulations.

Formulation is particularly important because differences in the absorption and systemic availability of curcuminoids may influence the magnitude of their effects on liver-related outcomes. Enhanced-delivery formulations, including phytosomal and nano-micelle preparations, have been specifically investigated in clinical studies involving patients with NAFLD. However, the use of different formulations also contributes to heterogeneity across trials, making it difficult to determine the optimal preparation and clinically effective dose. Overall, the current evidence supports further investigation of curcumin as a potential adjunctive approach for NAFLD, but larger and longer-term randomized controlled trials using standardized formulations and clinically relevant liver-specific outcomes, including validated measures of steatosis, inflammation, and fibrosis, are required before firm clinical conclusions can be drawn.

Implications for Future Research

Although the available evidence provides biological support for the potential hepatoprotective effects of curcumin, substantial uncertainty remains regarding the translation of preclinical findings into clinically meaningful benefits in patients with NAFLD.

a. Large-Scale, Multicenter Clinical Trials: Most studies are still animal-based or involve clinical trials with small sample sizes at limited locations. Broader human clinical trials are needed to verify the effects across diverse global populations (He *et al.*, 2024b)(Lamichhane, D. Y. Lee, *et al.*, 2024).
b. Enhancement of Bioavailability: Given that curcumin has low oral bioavailability, the development of novel delivery systems—such as Nanostructured Lipid Carriers (Cur-NLC)—requires continued optimization to ensure more effective distribution to the target organ (the liver) in humans (Hussain *et al.*, 2023).
c. Research on Advanced Stages (NASH and Fibrosis): Most current literature focuses on the early stages of NAFLD (simple steatosis). There is a significant opportunity to conduct in-depth research into curcumin's potential to reverse advanced liver fibrosis or prevent progression to cirrhosis and hepatocellular carcinoma (HCC) (Filipovic, Lukic, Mijac, Marjanovic-haljilji, *et al.*, 2021;He *et al.*, 2024c).
d. Metabolite Pharmacokinetics: Further research is needed to understand the functional roles of curcumin metabolites (such as tetrahydrocurcumin) in lipid metabolism and redox homeostasis within the human body (He *et al.*, 2024c).

Collectively, the available evidence supports further investigation of Curcuma longa and curcumin as potential adjunctive approaches for NAFLD, while the current evidence remains insufficient to establish them as standard therapy.

Limitations of the review. The evidence base was heterogeneous and included experimental, animal, and limited human studies, which differed in model, curcumin formulation, dose, treatment duration, and outcome assessment. The inclusion of indirect hepatoprotective models provides mechanistic context but should not be interpreted as direct evidence of clinical benefit in NAFLD. In addition, no single formal risk-of-bias instrument was applied across all heterogeneous study designs. These limitations reduce the certainty and direct clinical applicability of the overall findings.

CONCLUSION

The available evidence suggests that Curcuma longa and curcumin have biologically plausible hepatoprotective effects relevant to NAFLD, particularly through modulation of lipid metabolism, oxidative stress, inflammatory signaling, insulin sensitivity, and gut–liver pathways. However, the evidence is dominated by bioinformatics, in vitro, and animal studies, and these findings should not be interpreted as proof of clinical efficacy in patients. Limited randomized clinical studies indicate potential improvements in selected liver-related and metabolic outcomes, but heterogeneity in formulations, doses, treatment duration, sample sizes, and outcome measures prevents firm conclusions regarding therapeutic effectiveness. Curcumin may therefore be regarded as a promising adjunctive candidate for further investigation rather than an established NAFLD therapy. Future adequately powered, longer-duration randomized trials using standardized formulations and clinically relevant liver-specific outcomes, including validated measures of steatosis, inflammation, and fibrosis, are needed.

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