Herbal Bioactive Compounds as Emerging Therapeutics in Non-Alcoholic Fatty Liver Disease: A Comprehensive Review

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***Abstract*—non-alcoholic fatty liver disease (NAFLD), recently redefined as metabolic dysfunction–associated steatotic liver disease (MASLD), is now the most common chronic liver disorder worldwide, strongly linked with obesity, diabetes, dyslipidemia, and hypertension. Its pathogenesis follows the "multiple-hit" hypothesis, involving insulin resistance, lipotoxicity, oxidative stress, inflammation, gut dysbiosis, and genetic predisposition. Progression ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma, with fibrosis being the key predictor of outcomes. Diagnosis integrates laboratory markers, imaging techniques, non-invasive scoring systems, and, in selected cases, liver biopsy. With no FDA-approved drugs, lifestyle modification remains the primary treatment. Increasing evidence highlights nutraceuticals and bioactive compounds—such as curcumin, silymarin, resveratrol, omega-3 fatty acids, quercetin, and coenzyme Q10—for their antioxidant, anti-inflammatory, and lipid-modulating effects. Clinical and preclinical studies demonstrate improvements in liver enzymes, steatosis, and fibrosis, suggesting these agents as promising complementary therapies.**

***Index Terms*—Curcumin; Herbal bioactive compounds; Metabolic dysfunction–associated steatotic liver disease (MASLD); Metabolic syndrome; Non-alcoholic fatty liver disease (NAFLD); Nutraceuticals; Omega-3 fatty acids; Quercetin; Resveratrol; Silymarin.**

I. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), recently redefined as metabolic dysfunction–associated steatotic liver disease (MASLD) with its progressive subtype MASH, is now the leading cause of chronic liver disease worldwide. Its strong association with obesity, type 2 diabetes, dyslipidemia, and hypertension underscores its metabolic basis. Current guidelines emphasize risk stratification with non-invasive tests and lifestyle modification as the cornerstone of therapy, marking a shift from exclusion to inclusion criteria in diagnosis[1]–[3].

The global prevalence of NAFLD is estimated at 32%, with MASLD rapidly emerging as a major cause of cirrhosis and hepatocellular carcinoma. In India, the prevalence ranges from 9% to 45% in the general population, and up to 60% in individuals with metabolic syndrome, reflecting the country's dual burden of obesity and diabetes[4]–[6].

Despite its high prevalence, NAFLD remains underdiagnosed due to its silent course, often being detected incidentally during imaging or abnormal liver enzyme evaluation. Currently, there is no FDA-approved pharmacological therapy, and interventions rely heavily on weight reduction, dietary modification, and physical activity[7]–[9].

Emerging research has focused on the role of gut microbiota, oxidative stress, inflammation, and genetic predisposition in disease progression, paving the way for nutraceutical and herbal-based interventions. In particular, bioactive compounds such as curcumin, silymarin, and resveratrol have shown promise in ameliorating hepatic steatosis and improving metabolic parameters[10]–[12].

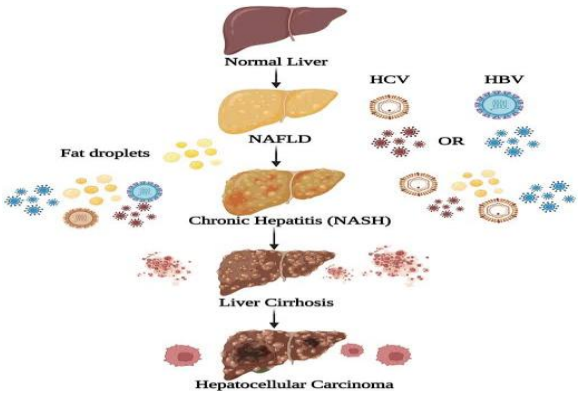

Figure 1: Spectrum of liver condition (Source: Sharma L et al., 2023)

This image shows the Different stages involved in the progression from normal liver to hepatocellular carcinoma (HCC).

II. GLOBAL BURDEN OF NAFLD

The prevalence of NAFLD has increased in parallel with rising obesity and type 2 diabetes, making it a global public health challenge. Currently, NAFLD affects approximately 1 in 3 adults worldwide, with the highest prevalence observed in the Middle East (32%) and South America (30%), followed by Asia (27%)[13]. In the United States, NAFLD prevalence is around 24%, with significant economic and healthcare implications[14].

In India, urbanization, sedentary lifestyles, and dietary transitions have significantly contributed to the escalating prevalence of NAFLD. Studies estimate that approximately 9–32% of the Indian population is affected, with higher prevalence in obese and diabetic individuals (up to 60%)[15–17]. Unlike Western populations, a considerable proportion of Indian NAFLD patients are non-obese, a phenomenon termed "lean NAFLD," attributed to genetic factors and increased visceral adiposity[18].NAFLD is not only confined to adults but is increasingly diagnosed in children and adolescents, paralleling the global rise in childhood obesity. Pediatric NAFLD prevalence is estimated at 7.6% in the general population and 34% among obese children[19].

The disease also poses a significant economic burden. In the United States, the direct medical costs of NAFLD are estimated at over $100 billion annually, while in Europe, it accounts for €35 billion. In India, the absence of dedicated cost analysis masks the true impact, but the rising prevalence suggests a looming public health crisis[20,21].

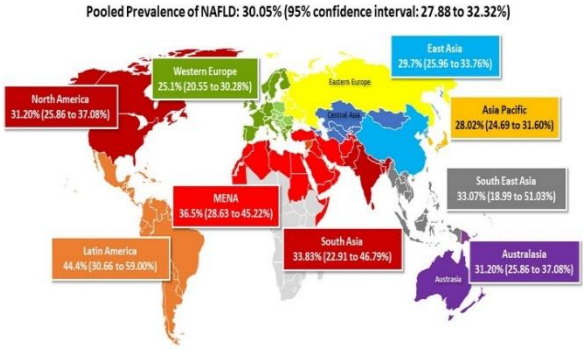

Figure 2: Global prevalence of NAFLD (Source: Younossi ZM et al., 2023)

This image shows the Global prevalence of non-alcoholic fatty liver disease (NAFLD) according to different regions based on data collected between 1990–2019. Prevalence rates are highest in the Middle East/North Africa (MENA) and Latin America, followed by South Asia, North America, Europe, and Asia-Pacific. The worldwide pooled prevalence is estimated at 30.05% (95% CI 27.38–32.25).

III. PATHOPHYSIOLOGY OF NAFLD/MASLD

The pathogenesis of NAFLD is multifactorial, involving a complex interplay of genetic, metabolic, and environmental factors. Traditionally, the "two-hit hypothesis" was proposed, with the first hit being hepatic fat accumulation due to insulin resistance, and the second hit involving oxidative stress and inflammation leading to NASH. However, this model has beenreplaced by the "multiple-hit hypothesis," which recognizes the contribution of lipotoxicity, gut microbiota, adipokines, and genetic predisposition[22,23].

3.1 Insulin Resistance And Lipid Metabolism

Insulin resistance is the central driver of NAFLD, leading to increased lipolysis, elevated free fatty acid flux to the liver, and enhanced de novo lipogenesis. This results in hepatic triglyceride accumulation, which sensitizes hepatocytes to oxidative injury and apoptosis[24,25].

3.2 Oxidative Stress and Mitochondrial Dysfunction

Excessive fatty acid oxidation in the liver generates reactive oxygen species (ROS), causing lipid peroxidation, mitochondrial dysfunction, and activation of inflammatory pathways. ROS also impair

insulin signaling, perpetuating a vicious cycle of steatosis and insulin resistance[26],[27].

3.3 Inflammation and Cytokine Release

Kupffer cells and infiltrating immune cells release proinflammatory cytokines such as TNF-α, IL-6, and IL-1β, which exacerbate hepatocellular damage. Chronic inflammation promotes stellate cell activation, extracellular matrix deposition, and fibrosis progression[28],[29].

3.4 Gut–Liver Axis

Dysbiosis and increased intestinal permeability result in the translocation of endotoxins such as lipopolysaccharide (LPS) into the portal circulation, activating Toll-like receptor pathways and amplifying hepatic inflammation[30],[31]. Short-chain fatty acids, bile acid metabolism, and microbial metabolites further modulate hepatic lipid and glucose homeostasis[32].

3.5 Genetic and Epigenetic Factors

Polymorphisms in genes such as PNPLA3, TM6SF2, and MBOAT7 have been strongly associated with susceptibility to NAFLD and disease progression. Epigenetic modifications including DNA methylation, histone modification, and non-coding RNAs also play key roles in regulating lipid metabolism and inflammatory responses[33]–[35].

3.6 Fibrosis Progression

Fibrosis is the strongest predictor of long-term outcomes in NAFLD. Hepatic stellate cell activation, driven by chronic inflammation, oxidative stress, and metabolic dysregulation, leads to extracellular matrix deposition. Over time, this progresses to bridging fibrosis, cirrhosis, and hepatocellular carcinoma[36],[37]

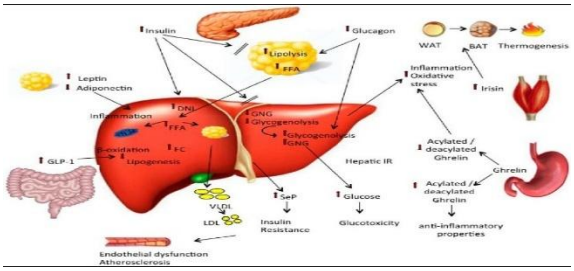

Figure 3: Pathophysiology of NAFLD/MASLD (Source: Huh JY et al., 2016)

This image is a schematic diagram highlighting the key metabolic players and main pathogenic pathways in NAFLD, including insulin resistance, adipokine changes, increased lipolysis, de novo lipogenesis, and hormonal regulation

IV. CLINICAL MANIFESTATIONS OF NAFLD/MASLD

Non-alcoholic fatty liver disease (NAFLD), now increasingly referred to as metabolic dysfunction-associated steatotic liver disease (MASLD), represents a spectrum of liver disorders strongly linked to obesity, insulin resistance, and metabolic syndrome[38]. The clinical course ranges from simple steatosis to progressive stages such as non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and eventually hepatocellular carcinoma (HCC). Disease progression depends on genetic predisposition, lifestyle, and environmental factors. Understanding the distinct stages is crucial for appropriate diagnosis, prognosis, and management of affected patients[38].

4.1 Simple Steatosis (NAFL):

Simple steatosis, also termed non alcoholic fatty liver (NAFL), is the earliest stage of the disease, defined by excessive triglyceride deposition in hepatocytes without significant necroinflammation or fibrosis[39]. Patients are usually asymptomatic, and the condition is often detected incidentally on imaging or through mild abnormalities in liver function tests. While simple steatosis is typically benign, the presence of metabolic risk factors such as obesity, dyslipidemia, or insulin resistance increases the likelihood of progression to more advanced liver injury[39].

4.2 Non-alcoholic Steatohepatitis (NASH):

Non-alcoholic steatohepatitis (NASH) is a more severe stage, characterized by hepatocyte ballooning, lobular inflammation, and varying degrees of fibrosis[40]. The inflammatory response differentiates NASH from simple steatosis, making it clinically significant. Patients with NASH face higher risks of progression to cirrhosis and liver-related complications. Moreover, NASH is strongly associated with systemic disorders, including cardiovascular disease and type 2 diabetes mellitus, both of which increase overall morbidity and mortality. Thus, NASH is considered a crucial therapeutic target in NAFLD[40].

4.3 Fibrosis and Cirrhosis:

Fibrosis represents the liver's wound-healing response to persistent inflammation, primarily driven by hepatic stellate cell activation and deposition of extracellular matrix proteins[41]. As fibrosis advances, normal hepatic architecture becomes distorted, leading to cirrhosis. Cirrhosis is characterized by portal hypertension,

impaired synthetic capacity, and the risk of decompensated complications such as ascites, variceal bleeding, or hepatic encephalopathy. Cirrhosis is also the strongest predictor of liver-related mortality in NAFLD. Timely identification of fibrosis stages is essential for patient risk stratification and management[41].

4.4 Hepatocellular Carcinoma (HCC):

NAFLD has emerged as a leading cause of hepatocellular carcinoma (HCC), with cases increasingly reported in both cirrhotic and non-cirrhotic patients[42]. The mechanisms involve lipotoxicity, oxidative stress, and chronic low-grade inflammation, along with genetic and epigenetic changes. Rising global rates of obesity and diabetes have contributed significantly to the burden of NAFLD-associated HCC. Importantly, HCC in NAFLD may develop silently without preceding cirrhosis, complicating screening strategies and highlighting the need for enhanced surveillance protocols and preventative approaches[42].

4.5 Laboratory Findings

Biochemical testing often reveals mild to moderate elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), although these abnormalities are nonspecific[43]. The AST/ALT ratio typically remains below one in early disease but may reverse as fibrosis progresses[43]. Additional laboratory indicators such as elevated serum ferritin, cytokeratin-18 fragments, altered lipid metabolism, and glucose intolerance are supportive markers of metabolic dysfunction. However, these parameters alone cannot establish a definitive diagnosis, highlighting the need for integration with imaging and non-invasive scoring tools[44].

4.5.1 Imaging Modalities

Several imaging methods are utilized in the diagnostic evaluation of NAFLD. Ultrasonography is the most commonly used initial tool, able to detect hepatic steatosis when at least 20% of hepatocytes are affected, though sensitivity decreases in obese individuals[45]. Transient elastography (FibroScan) is widely applied to assess liver stiffness and quantify fat using the controlled attenuation parameter (CAP), providing non-invasive evaluation of both fibrosis and steatosis[46]. Magnetic resonance imaging–proton density fat fraction (MRI-PDFF) remains the gold standard for fat quantification but is limited by high cost[47].

4.5.2 Non-Invasive Scoring Systems

To minimize the need for invasive biopsy, several validated scoring systems have been developed. The NAFLD Fibrosis Score (NFS) and the Fibrosis-4 (FIB-4) index are commonly used, combining age, body mass index, aminotransferase levels, and platelet count to estimate fibrosis severity[48]. These tools are effective in ruling out advanced disease but less precise in intermediate cases. The Enhanced Liver Fibrosis (ELF) test, based on serum biomarkers of fibrogenesis, is increasingly recognized as a valuable method for stratifying patient risk and guiding follow-up[49].

4.5.3 Liver Biopsy

Despite advances in non-invasive techniques, liver biopsy continues to serve as the reference standard for NAFLD diagnosis and staging[50]. It provides detailed histological information, including the degree of steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis. Biopsy allows definitive distinction between simple steatosis and nonalcoholic steatohepatitis, which has greater prognostic significance. Nevertheless, its routine use is limited by invasiveness, procedural risks, cost, and potential sampling error. Currently, biopsy is reserved for patients with uncertain diagnosis or those at high risk of advanced disease[50].

Table 1. NASH Clinical Research Network histological scoring system

NAFLD activity score	NASH fibrosis stage
Steatosis < 5%: 0 5–33%: 1 34–66%: 2 > 66%: 3 **Lobular inflammation** None: 0 < 2: 1 2–4: 3 > 4: 4 **Ballooning of hepatocytes** None: 0 Few ballooned: 1 Many ballooned: 2 **NAS score (0–8)** < 3: not NASH ≥ 5: NASH	**Stage 0** No fibrosis **Stage 1** **Zone 3 perisinusoidal fibrosis** • Mild – 1a • Moderate – 1b • Portal/periportal – 1c **Stage 2** Perisinusoidal and portal/ periportal fibrosis **Stage 3** Bridging fibrosis **Stage 4** Cirrhosis

Figure 4: Clinical manifestations of NAFLD/MASLD (Source: Rizzo et al., 2023)

This figure summarizes the spectrum of clinical presentations in NAFLD, ranging from asymptomatic hepatic steatosis to advanced stages such as nonalcoholic steatohepatitis, progressive fibrosis, cirrhosis, and hepatocellular carcinoma. Symptoms are often non-specific, with many cases detected incidentally during routine liver function tests or imaging.

V. ROLE OF NUTRACEUTICALS AND BIOACTIVE COMPOUNDS IN THE MANAGEMENT OF NAFLD

Nutraceuticals and bioactive compounds have gained significant attention in the prevention and management of non-alcoholic fatty liver disease (NAFLD). These compounds exert beneficial effects primarily through antioxidant, anti-inflammatory, and lipid-modulating properties.

Curcumin, the active component of turmeric, has been shown to improve liver function, metabolic profile, and body composition in NAFLD patients, with evidence from systematic reviews and meta-analyses confirming its hepatoprotective role[38]. Similarly, silymarin, particularly when combined with vitamin E, demonstrated positive effects on liver enzymes and histological parameters in clinical trials[37],[55].

Resveratrol, a polyphenolic compound, exerts its therapeutic effects by activating AMP-activated protein kinase (AMPK), thereby improving lipid metabolism and reducing hepatic fat accumulation[49].

Vitamin E supplementation also plays a pivotal role in reducing oxidative stress and improving liver histology, making it one of the most widely recommended nutraceuticals for NAFLD[55].

Omega-3 fatty acids have been shown to regulate hepatic lipid metabolism and reduce triglyceride accumulation, with clinical and meta-analytical evidence supporting their efficacy in NAFLD management[27],[28]. Similarly, betaine supplementation improves hepatic insulin resistance and prevents steatosis, contributing to its hepatoprotective properties[30].

Polyphenols such as chlorogenic acid and quercetin exhibit strong antioxidant and anti-inflammatory actions, with both animal and clinical studies suggesting their potential in managing metabolic dysfunction-associated steatotic liver disease (MASLD)[53],[38]. Green tea polyphenols, particularly epigallocatechin gallate (EGCG), also demonstrate protective roles by reducing oxidative stress and improving hepatic fat metabolism[10]. Furthermore, systematic reviews highlight the broad potential of polyphenol interventions in ameliorating NAFLD progression[10].

Other nutraceuticals such as coenzyme Q10[57], berberine[29], and lycopene[31] have also been reported to exert beneficial effects by modulating liver enzymes, reducing systemic inflammation, and combating oxidative stress. Collectively, these findings indicate that nutraceuticals and bioactive compounds can serve as complementary therapeutic options for NAFLD, though large-scale randomized controlled trials are warranted for stronger clinical validation.

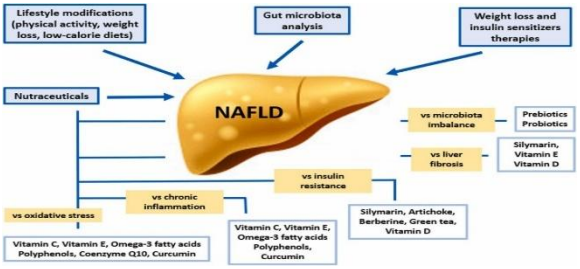

Figure 5 : Complementary approaches to NAFLD and main target of nutraceuticals (Source: Rizzo M et al., 2023)

This diagram illustrates various adjunctive strategies for managing NAFLD, focusing on how nutraceuticals target key pathophysiological pathways such as insulin resistance, lipid accumulation, oxidative stress, inflammation, and gut dysbiosis. The figure highlights the multi-targeted potential of bioactive compounds as part of an integrated therapeutic approach.

VI. MECHANISMS OF ACTION OF HERBAL BIOACTIVE COMPONENTS IN NAFLD

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6.1 Antioxidant Activity

Oxidative stress is central to NAFLD progression, as lipid peroxidation and reactive oxygen species (ROS) trigger hepatocyte injury and fibrogenesis. Polyphenolic compounds such as curcumin, quercetin, resveratrol, chlorogenic acid, and anthocyanins act as potent antioxidants by scavenging free radicals, enhancing endogenous antioxidant defenses (e.g., glutathione, superoxide dismutase), and reducing lipid peroxidation[35],[53]. Silymarin also stabilizes hepatocyte membranes and reduces ROS-mediated injury, thereby preventing oxidative DNA and protein damage[37].

6.2 Anti-inflammatory Effects

Chronic low-grade inflammation is a hallmark of NAFLD. Curcumin, quercetin, and resveratrol suppress nuclear factor-kappa B (NF-κB) signaling, leading to reduced transcription of proinflammatory cytokines such as TNF-α, IL-6, and IL-1β[10],[53]. Silymarin and berberine attenuate Kupffer cell activation and inhibit inflammatory cascades[37],[29]. EGCG, the principal catechin in green tea, exerts anti-inflammatory activity through downregulation of MAPK and NF-κB pathways[10].

6.3 Regulation of Lipid Metabolism

Excess hepatic lipid accumulation results from increased fatty acid influx, de novo lipogenesis, and impaired oxidation. Resveratrol and quercetin activate AMP-activated protein kinase (AMPK), enhancing fatty acid β-oxidation and suppressing lipogenesis[34],[53]. Omega-3 fatty acids reduce hepatic triglyceride levels by modulating PPAR-α and SREBP-1c pathways[27]. Betaine reduces hepatic lipid load by promoting very-low-density lipoprotein (VLDL) secretion and enhancing phosphatidylcholine synthesis[30]. Curcumin similarly decreases expression of lipogenic transcription factors, further reducing steatosis[38].

6.4 Improvement of Insulin Sensitivity

Insulin resistance is a key driver of hepatic steatosis. Curcumin, berberine, and quercetin enhance insulin sensitivity by upregulating glucose transporter 4 (GLUT4) and improving insulin receptor signaling[10],[29],[53]. Resveratrol activates SIRT1 and AMPK, leading to improved glucose homeostasis and reduced hepatic fat accumulation[34]. Omega-3 fatty acids reduce systemic inflammation, indirectly improving insulin sensitivity[27].

6.5 Antifibrotic Actions

Progression of NAFLD to non-alcoholic steatohepatitis (NASH) and cirrhosis is driven by hepatic stellate cell (HSC) activation and extracellular matrix deposition. Silymarin, curcumin, and resveratrol suppress HSC activation by modulating transforming growth factor-β (TGF-β) signaling and reducing collagen synthesis[37],[34],[38]. EGCG prevents fibrosis progression by inhibiting oxidative stress–induced stellate cell activation[10]. Anthocyanins and chlorogenic acid also demonstrate antifibrotic effects in preclinical studies[53].

6.6 Modulation of the Gut–Liver Axis

Gut dysbiosis contributes to NAFLD via increased intestinal permeability, endotoxin translocation, and altered bile acid signaling. Polyphenols such as quercetin, chlorogenic acid, and anthocyanins restore gut microbial diversity and reduce lipopolysaccharide (LPS) translocation[53]. Berberine exerts prebiotic-like effects by enriching short-chain fatty acid–producing bacteria, thereby improving metabolic and

inflammatory profiles[29]. EGCG has also been shown to modulate gut microbiota and bile acid metabolism, further protecting against steatosis[10].

6.7 Mitochondrial Protection and Energy Homeostasis

Mitochondrial dysfunction plays a central role in NAFLD-related oxidative stress and impaired β-oxidation. Coenzyme Q10, a key electron transport chain component, improves mitochondrial bioenergetics and reduces ROS production[35]. Curcumin and resveratrol enhance mitochondrial biogenesis through activation of PGC-1α and SIRT1[34],[38]. Lycopene also stabilizes mitochondrial membranes and prevents oxidative injury[31].

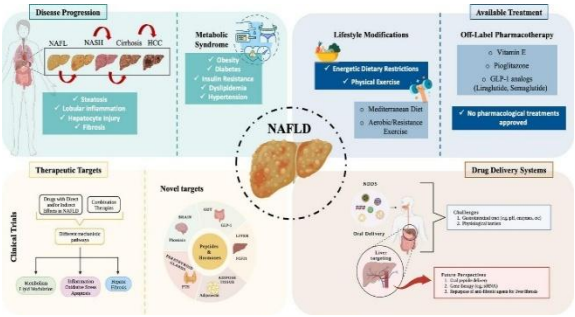

Figure 6: Mechanisms of action of herbal bioactive components in NAFLD (Source: Domingues I et al., 2023)

This figure summarizes the multifaceted ways in which herbal bioactive compounds mitigate NAFLD progression, including antioxidant activity, anti-inflammatory effects, improvement of insulin sensitivity, regulation of lipid metabolism, modulation of the gut–liver axis, and prevention of fibrosis. The illustration highlights key molecular targets and pathways influenced by plant-derived nutraceuticals.

VII. EVIDENCE FROM PRECLINICAL AND CLINICAL STUDIES

Herbal bioactive compounds have been extensively investigated in both animal models and human trials for their therapeutic effects in non-alcoholic fatty liver disease (NAFLD). Preclinical studies provide mechanistic insights, while clinical trials highlight translational potential and limitations.

7.1 Preclinical Evidence

Rodent models fed high-fat or high-fructose diets are widely employed to replicate the metabolic and hepatic disturbances observed in human NAFLD. These models develop hepatic steatosis, insulin resistance, oxidative stress, and low-grade inflammation, making them valuable for investigating disease mechanisms. They also provide an experimental platform to evaluate the hepatoprotective potential of dietary bioactive compounds. Through such models, researchers can examine molecular pathways, therapeutic targets, and translational relevance of interventions aimed at preventing NAFLD progression.

7.1.1 Curcumin

Curcumin, the active polyphenol in turmeric, has been extensively studied in high-fat diet–induced NAFLD models. It significantly reduced hepatic lipid accumulation, oxidative stress, and pro-inflammatory cytokine expression, thereby protecting against steatohepatitis[38]. Mechanistically, curcumin activated AMP-activated protein kinase (AMPK), which promotes fatty acid oxidation, while simultaneously downregulating genes involved in de novo lipogenesis[10]. Through these combined actions, curcumin improved insulin sensitivity, reduced hepatic injury, and demonstrated broad hepatoprotective effects, highlighting its therapeutic potential in preventing disease progression in experimental NAFLD[10].

7.1.2 Silymarin

Silymarin, derived from Silybum marianum (milk thistle), has shown strong antioxidant and antifibrotic properties in rodent models of fatty liver disease[37]. By scavenging reactive oxygen species and inhibiting lipid peroxidation, silymarin effectively reduces hepatocellular oxidative stress. Additionally, it suppresses hepatic stellate cell activation, a key driver of fibrosis, thereby limiting fibrogenesis and slowing disease progression. These effects prevent the transition from simple steatosis to steatohepatitis, supporting its role as a liver-protective compound and justifying its evaluation in both experimental and clinical settings[37].

7.1.3 Resveratrol

Resveratrol, a natural polyphenol found in grapes and berries, exerts hepatoprotective effects through regulation of metabolic and inflammatory pathways. In obese and high-fat diet–fed mice, resveratrol alleviated hepatic steatosis and improved insulin sensitivity by activating sirtuin-1 (SIRT1) and AMPK signaling[34]. These pathways enhance fatty acid oxidation, reduce lipogenesis, and improve mitochondrial function. Resveratrol also demonstrated

anti-inflammatory actions, reducing cytokine production and oxidative stress. Together, these multifaceted mechanisms highlight resveratrol as a promising therapeutic agent in NAFLD management[34].

7.1.4 Quercetin

Quercetin, a flavonoid abundant in fruits and vegetables, reduces hepatic steatosis by modulating mitochondrial activity and inflammatory signaling pathways. In rodent NAFLD models, it lowered liver fat accumulation and attenuated hepatic inflammation by suppressing NF-κB–mediated cytokine expression[53]. Quercetin also enhanced mitochondrial function and energy metabolism, which improved hepatocyte resilience against lipotoxicity. These combined effects prevent the progression from fatty liver to more advanced disease stages, demonstrating its importance as a multi-targeted compound with both metabolic and anti-inflammatory benefits[53].

7.1.5 Epigallocatechin Gallate (EGCG)

Epigallocatechin gallate (EGCG), the major catechin in green tea, exhibits potent antioxidant and metabolic regulatory effects. In diet-induced NAFLD rodent models, EGCG reduced hepatic lipid accumulation, promoted fatty acid oxidation, and suppressed inflammatory responses[10]. Additionally, EGCG improved intestinal barrier function, reducing endotoxin leakage from the gut and subsequent hepatic inflammation. These combined hepatic and extrahepatic actions highlight EGCG's potential as a natural therapeutic candidate for NAFLD prevention and treatment, with benefits extending to metabolic and gut-liver axis regulation[10].

7.1.6 Berberine

Berberine, an alkaloid derived from medicinal plants, demonstrated significant hepatoprotective effects in high-fat diet mouse models of NAFLD[29]. It lowered hepatic triglyceride levels, improved glucose homeostasis, and enhanced insulin sensitivity by regulating lipid and carbohydrate metabolism. Moreover, berberine modulated gut microbiota composition, restoring microbial balance and reducing systemic inflammation. Through simultaneous actions on hepatic metabolism and the gut-liver axis, berberine emerged as an effective multi-target agent capable of attenuating both metabolic dysfunction and hepatic injury in experimental NAFLD[29].

7.2 Clinical Evidence

Several randomized controlled trials (RCTs) and meta-analyses have evaluated the efficacy of herbal bioactives in NAFLD patients.

7.2.1 Curcumin

Curcumin has been evaluated in several randomized controlled trials for its hepatoprotective effects. A double-blind RCT using phytosomal curcumin (500 mg/day) for eight weeks demonstrated significant improvements in hepatic fat content, serum ALT and AST levels, and body mass index compared to placebo[38]. Beyond this, a meta-analysis confirmed reductions in liver enzymes and improvements in lipid metabolism, strengthening evidence for its clinical use in NAFLD management[38]. These findings support curcumin as a promising adjunctive therapeutic option for patients

7.2.2 Silymarin

Silymarin, derived from Silybum marianum, has shown therapeutic benefits in human trials of NAFLD. Clinical studies report consistent reductions in serum aminotransferases, suggesting improved hepatocellular function[37]. Histological findings also indicate reduced fat accumulation and inflammatory activity, particularly when silymarin is combined with vitamin E supplementation[37]. Its strong antioxidant and antifibrotic mechanisms observed in preclinical models appear translatable to patients, though results vary based on dosage and duration. Collectively, these studies highlight silymarin as a clinically useful hepatoprotective compound.

7.2.3 Resveratrol

Resveratrol supplementation has been explored in clinical trials for its effects on metabolic and inflammatory pathways in NAFLD patients. At a dosage of 500 mg/day for 12 weeks, resveratrol significantly reduced inflammatory cytokines and liver enzyme levels, reflecting improved hepatic function[34]. However, its impact on hepatic steatosis remains inconsistent across different studies, possibly due to differences in formulation or patient populations[34]. Despite this variability, the evidence suggests resveratrol exerts beneficial systemic effects that may indirectly improve long-term liver outcomes.

7.2.4 Omega-3 Fatty Acids

Omega-3 polyunsaturated fatty acids are among the most widely studied bioactives in NAFLD. Meta-analyses consistently demonstrate significant reductions in serum triglycerides, a key metabolic risk factor, along with improvements in hepatic steatosis

detected by imaging modalities[27],[28]. Their anti-inflammatory and lipid-modulating properties support their use as adjunctive therapy, particularly in patients with dyslipidemia[27]. While omega-3 fatty acids are not curative, they provide metabolic benefits that complement lifestyle interventions, making them a clinically relevant component of NAFLD management strategies.

7.2.5 Betaine

Betaine, a naturally occurring methyl donor, has demonstrated clinical efficacy in controlled NAFLD trials. Patients receiving betaine exhibited improvements in hepatic steatosis and insulin resistance, suggesting enhanced metabolic regulation[30]. However, its effects on fibrosis remain uncertain, with limited evidence supporting structural reversal of advanced disease[30]. Betaine's beneficial role likely stems from its ability to enhance hepatic methylation capacity and modulate lipid metabolism. These findings indicate potential utility, though additional long-term studies are required to establish its therapeutic significance.

7.2.6 Coenzyme Q10

Coenzyme Q10, an essential mitochondrial cofactor with antioxidant properties, has been tested in NAFLD patients. Supplementation at 100 mg/day for 12 weeks significantly reduced serum ALT and AST concentrations, markers of hepatic injury, while also lowering oxidative stress indicators[35]. Improvements in systemic inflammation were also noted, reflecting broader metabolic benefits. Despite encouraging results, trial sizes remain small and heterogeneity in design limits definitive conclusions[35]. Nevertheless, coenzyme Q10 shows potential as an adjunctive therapy supporting mitochondrial and hepatic function.

7.2.7 Berberine

Berberine has gained attention through clinical trials, particularly within Chinese cohorts, for its metabolic and hepatic benefits in NAFLD patients. Findings demonstrate significant reductions in hepatic fat accumulation, improvements in insulin sensitivity, and favorable modulation of lipid profiles[29]. Additional benefits include enhanced glucose regulation and reduction of systemic inflammation[29]. These effects align with preclinical evidence of berberine's action on hepatic metabolism and the gut-liver axis. Collectively, clinical studies validate berberine as a promising multi-targeted therapy for NAFLD.

7.3 Integrative Note

Despite encouraging results across multiple trials, variability in dosage, formulations, and study duration creates challenges in drawing firm conclusions. Many bioactives show benefits in liver enzymes, metabolic parameters, or histological features, but consistency across studies is lacking. Larger, multicenter randomized trials are required for validation. Taken together, preclinical and clinical evidence supports hepatoprotective potential, with animal models showing robust efficacy while human studies highlight variability. Nonetheless, convergence of findings underscores their promise as adjunct therapies in NAFLD management.

VIII. EXTRACTION OF THE BIOACTIVE COMPONENTS

8.1 Curcumin

Curcumin is extracted from turmeric by first cleaning and drying the rhizomes, which are then powdered and treated with ethanol, methanol, or acetone as the solvent. The mixture is left with gentle stirring for hours, filtered, and concentrated by evaporation. Final purification uses repeated crystallization or column chromatography. Advanced methods like Soxhlet extraction and pressurized liquid extraction are often used in commercial and pharmaceutical production for their higher yield and improved purity[67–69].

8.2 Silymarin (Milk Thistle)

Extraction of silymarin from milk thistle seeds typically involves a two-step process, starting with defatting the seeds using n-hexane. The defatted meal is subsequently subjected to methanol or acetone extraction under reflux. The filtered and evaporated extract is purified by repeated crystallization or column chromatography, and pressurized liquid extraction can further increase efficiency and yield[70–71].

8.3 Resveratrol

Resveratrol is isolated from grapes or *Polygonum cuspidatum* using enzyme-assisted extraction, which involves hydrolyzing plant powders with cellulase and then extracting with ethanol under reflux. After filtration and concentration, the resveratrol is crystallized and purified. Green, low-temperature methods preserve resveratrol bioactivity and are favored in nutraceutical applications[72–73].

8.4 Quercetin

Quercetin is obtained from dried and powdered onion skins, apple peels, or kale using ethanol, methanol, or acetone. The mixture is stirred or sonicated, filtered, and the solvent is removed under reduced pressure. Chromatographic purification ensures high antioxidant content. Ethanol (80%) is generally preferred for safety and effectiveness, with onion skins yielding especially high quercetin content[74–75].

8.5 EGCG (Green Tea)

EGCG extraction from green tea involves removal of caffeine, followed by extraction with solvents (often water, ethyl acetate, or butanol), and purification using silica gel column chromatography. Modern techniques like membrane distillation and macroporous resin improve isolation, offering purities over 97% and maintaining antioxidant properties for supplements[76–77].

8.6 Berberine

Berberine is extracted from roots and stems of Berberis and goldenseal using ethanol, methanol, or chloroform. Soxhlet and cold maceration are common, with shade drying and mild temperatures enhancing stability. The concentrated extract is further purified via crystallization, making the product suitable for both pharmaceuticals and herbal therapies[78–79].

8.7 Omega-3 Fatty Acids (EPA/DHA)

Omega-3 fatty acids, particularly EPA and DHA, are extracted from plant oils like perilla using supercritical CO_2 extraction at high pressures (200–300 bar) and 40–60°C temperatures. Lyophilizing the plant material before extraction increases yield, and this eco-friendly approach is highly scalable for commercial production[80].

8.8 Anthocyanins

Anthocyanins from *Clitoria ternatea* and other flowers are extracted using microwave-assisted extraction or hydroalcoholic methods (ethanol/water at 60°C). Proper adjustment of solvent ratios and extraction time guarantees high anthocyanin recovery. Ethanol is preferred for its effectiveness, and gentle techniques maintain antioxidant activity for food and cosmetic use[81–82].

8.9 Betaine

Betaine is obtained from beetroot and herbal sources using acidified methanol extraction followed by rotary evaporation and crystallization. Alternatively, reactive extraction with organic solvents provides phase separation and higher purification, making the resulting betaine suitable for pharmaceutical and food industry applications[83].

8.10 Chlorogenic Acid

Chlorogenic acid is extracted from coffee beans, artichoke, and herbal sources using ethanol–water solvent systems or supercritical CO_2 extraction. Key parameters include extraction temperature and pH, which influence maximum yield and purity. These methods are also used in green and functional foods industries[84].

8.11 Lycopene

Extraction of lycopene from tomato and watermelon utilizes solvents such as acetone, hexane, or ethanol on dried and pulverized fruit. Repeated extraction and column chromatography further concentrate lycopene, ensuring purity and stability for use in food, cosmetic, and nutraceutical products[85].

8.12 Vitamin E

Vitamin E (tocopherol) is recovered from seeds and nuts using hexane or ethanol solvents, followed by filtration and purification through chromatography. Extraction and processing under reduced oxygen conditions secure the stability and bioavailability of the final tocopherol product for use in supplements[86].

8.13 Coenzyme Q10

Production of CoQ10 typically involves fermenting yeast or bacteria, followed by extraction with hexane or ethanol and crystallization or chromatography to purify the final product. These methods yield high-quality CoQ10 for medical and nutritional use[87].

8.14 Polyphenols

Polyphenols from fruits, vegetables, and tea are isolated using water or ethanol-based extraction methods, often enhanced by ultrasound or pressurized liquids. This technology increases extraction efficiency and reduces degradation, producing bioactive polyphenol-rich extracts for health-promoting products and functional foods[88].

IX. CONCLUSION

Nonalcoholic fatty liver disease (NAFLD) is a complex and multifactorial condition linked to obesity, insulin resistance, dyslipidemia, and lifestyle factors. Despite significant progress in understanding its pathogenesis, effective pharmacological interventions remain limited. This has generated growing interest in herbal bioactive compounds as potential therapeutic agents.

As summarized in previous chapters, bioactives such as curcumin, resveratrol, silymarin, epigallocatechin gallate, berberine, and quercetin demonstrate pleiotropic mechanisms including antioxidant, anti-inflammatory, insulin-sensitizing, antifibrotic, and gut microbiota–modulating effects. Evidence from preclinical studies consistently shows hepatoprotective effects, while clinical trials provide promising—yet often inconsistent—results.

Key challenges that hinder translation into clinical practice include poor bioavailability, variability in formulations and dosages, lack of long-term and large-scale randomized controlled trials, and limited standardization of outcome measures. Addressing these barriers is essential for advancing herbal bioactives as validated therapies.

The future of NAFLD management may benefit from novel formulations and delivery systems that enhance bioactive absorption and stability, including nanoparticle-based carriers, phytosomes, and functional food innovations. Pellet-based delivery systems, in particular, represent a promising strategy for ensuring controlled release, improved bioavailability, and patient compliance.

In conclusion, herbal bioactives offer multi-targeted benefits and hold substantial potential as adjunctive strategies in NAFLD management. Integration with dietary and lifestyle interventions, along with continued research into formulation technologies and rigorous clinical validation, will determine their role in future therapeutic landscapes.

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XII. AUTHOR CONTRIBUTION STATEMENT

Keerthana H (corresponding author) conceptualized the study and coordinated the drafting of the manuscript. Shamiksha, Bibin Chandru, Dsharani Priya, and Vignesh A contributed to literature review, data collection, and organization of sections. All authors contributed to the discussion of methodology and results, reviewed, and approved the final version of the manuscript.

XIII. CONFLICT OF INTEREST

Conflict of interest declared none.

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