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REVIEW ARTICLE

Mechanistic Insights and Clinical Evidence for Silymarin in the Management of Metabolic Dysfunction–Associated Fatty Liver Disease

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ABSTRACT: Metabolic dysfunction-associated fatty liver disease (MAFLD) represents a growing global health challenge, characterized by hepatic steatosis, inflammation, and fibrosis in the setting of metabolic syndrome. Its pathogenesis is driven by insulin resistance, disordered lipid metabolism, and oxidative stress, often progressing to steatohepatitis (MASH) and cirrhosis. Silymarin, a flavonoid-rich extract derived from *Silybum marianum*, has attracted considerable interest for its multi-target hepatoprotective properties. This review summarizes the pharmacological mechanisms by which silymarin exerts antioxidant, anti-inflammatory, anti-fibrotic, and lipid-modulating effects, thereby addressing key pathways in MAFLD development. Clinical evidence indicates that silymarin, particularly in bioavailable complex formulations, significantly improves liver enzyme profiles, lipid parameters, and imaging findings in MAFLD patients. Combination regimens with agents such as vitamin E or statins appear to enhance therapeutic efficacy. Despite promising data, broader clinical adoption requires further large-scale, rigorous trials to standardize dosing, confirm long-term benefits, and validate safety in heterogeneous patient populations. Overall, silymarin emerges as a promising adjunctive natural compound in the integrated management of MAFLD.

Keywords: Metabolic dysfunction-associated fatty liver disease, silymarin, hepatoprotection, oxidative stress, insulin resistance, clinical trials.

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1. INTRODUCTION

Metabolic dysfunction-associated fatty liver disease (MAFLD) represents a profound shift in our understanding of chronic liver conditions, moving beyond simple steatosis to recognize a highly heterogeneous disease intrinsically linked to systemic metabolic dysfunction [1]. This dysfunction encompasses a cluster of interrelated conditions including central obesity, elevated blood pressure, dyslipidemia, and impaired glucose metabolism, ranging from insulin resistance to overt type 2 diabetes mellitus. The global prevalence of MAFLD is rising at an alarming rate, mirroring the worldwide epidemics of obesity and metabolic syndrome, and now constitutes a major threat to public health security while imposing a staggering economic burden on healthcare systems [2]. This escalating prevalence underscores an urgent, unmet need for effective therapeutic strategies. The current pharmacological landscape remains notably sparse; the U.S. Food and Drug Administration has granted approval for only one drug, Resmetirom, specifically targeted for patients with moderate-to-severe metabolic dysfunction-associated steatohepatitis (MASH), and its use mandates concurrent commitment to diet and exercise modification [3, 4]. This limited armamentarium highlights the critical necessity to explore and validate additional treatment avenues.

The pathogenesis of MAFLD is deeply rooted in

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modern lifestyle patterns, with poor dietary habits serving as a primary driver. The excessive consumption of calories, particularly from processed foods high in sugars and saturated fats, coupled with irregular eating patterns and nutritionally imbalanced diets, exhibits a strong and dose-dependent association with the rising incidence of the disease [5]. For many years, hepatic steatosis was perceived as a relatively benign and static condition. However, a compelling and growing body of evidence has fundamentally overturned this view. MAFLD is now recognized as a multisystem disorder with far-reaching consequences. It is not merely a liver-specific issue but is independently associated with an elevated risk of cardiovascular disease, chronic kidney disease, obstructive sleep apnea, and certain extrahepatic malignancies, affecting the endocrine, circulatory, urinary, locomotor, and respiratory systems. This broad systemic impact definitively establishes MAFLD as a serious medical condition that significantly compromises overall health and accelerates morbidity, solidifying its status as a paramount global public health challenge [1]. Consequently, the development of safe and effective strategies for early intervention and treatment is not just important but crucial for mitigating its long-term individual and societal consequences.

The complex pathophysiology of MAFLD creates a challenging therapeutic target, as it involves a tangled network of metabolic insults including insulin resistance, chronic low-grade inflammation, lipotoxicity, mitochondrial dysfunction, and oxidative stress. This multifaceted nature suggests that agents with pleiotropic mechanisms of action may offer a strategic advantage over single-target approaches. It is within this context that silymarin, a natural flavonoid complex extracted from the seeds of the milk thistle plant (*Silybum marianum* (L.) Gaertn.), demands renewed and rigorous scientific attention. Historically used as a folk remedy, *Silybum marianum* originated in Southern Europe and North Africa [6, 7] and was introduced to China in 1972, with subsequent cultivation established in the northwest, northeast, and northern regions [8, 9]. The extract, silymarin, is composed chiefly of flavonolignans including silybin, silydianin, and silychristin, and has been documented to possess a wide spectrum of biological activities pertinent to liver health. These include the protection of hepatocyte membranes, promotion of hepatocyte regeneration, inhibition of hepatic stellate cell activation and fibrosis, scavenging of reactive oxygen species, attenuation of lipid peroxidation, and modulation of dysregulated lipid metabolism [10]. The novelty of this review lies in its focused synthesis of contemporary evidence positioning silymarin not merely as a general hepatoprotectant, but as a multi-target therapeutic agent whose specific antioxidant, anti-inflammatory, anti-fibrotic, and metabolic-regulating mechanisms directly counter the key pathological pillars of MAFLD, offering a complementary strategy that addresses the disease's complexity in ways single-pathway pharmaceuticals often cannot.

Despite this promising pharmacological profile, a significant hurdle has historically limited silymarin's clinical translation: its inherently poor aqueous solubility and consequent low oral bioavailability, which results in incomplete gastrointestinal absorption and suboptimal systemic delivery [10]. This pharmacokinetic challenge has often prevented the compound from exerting its full therapeutic potential in clinical settings. Therefore, critically investigating and elucidating its precise mechanisms of hepatoprotection and anti-inflammatory action, while simultaneously exploring advanced formulations designed to enhance its bioavailability, becomes a research imperative. This paper aims to provide a comprehensive and detailed review of the recent research progress on silymarin in the context of MAFLD treatment [11]. It will synthesize current understanding of its epidemiology and pathogenesis, systematically elaborate on the pharmacological mechanisms through which silymarin may confer benefit, evaluate the accumulating clinical evidence from human trials, and discuss future directions for optimizing its role in the management of this pervasive metabolic liver disease.

2. MAFLD EPIDEMIOLOGY, PATHOGENESIS AND DIAGNOSIS

2.1. Updated Diagnostic Criteria for MAFLD

Metabolic dysfunction-associated fatty liver disease (MAFLD) represents a significant evolution in the conceptualization of chronic liver conditions historically grouped under the term non-alcoholic fatty liver disease (NAFLD). It is defined as a clinicopathological syndrome characterized by excessive triglyceride accumulation within hepatocytes (hepatic steatosis), occurring in the context of underlying metabolic dysregulation. This definition marks a pivotal shift from its predecessor, NAFLD, which was principally an exclusionary diagnosis requiring the absence of significant alcohol consumption and other known causes of liver injury [12]. The disease spectrum encapsulated by MAFLD is broad and progressive, encompassing a continuum from isolated, simple hepatic steatosis to the necroinflammatory and fibrotic state of metabolic dysfunction-associated steatohepatitis (MASH), and ultimately to MASH-related cirrhosis and its complications, including hepatocellular carcinoma [1]. This progression is visually summarized in Figure 1, which schematically illustrates the transition from a healthy liver through stages of fat accumulation (MAFLD), inflammation and injury (MASH), fibrosis, and finally to hepatocellular carcinoma, providing a clear conceptual model of disease advancement.

The historical context of this disease entity is crucial for understanding the modern diagnostic paradigm. The term NAFLD was first introduced in 1980 by Jurgen Ludwig and colleagues, but for many years thereafter, simple fatty liver was largely perceived as a benign and incidental finding, leading to a prolonged period of limited intensive research into its diagnosis, risk stratification, and management [13]. This perspective began to change meaningfully around the turn of the 21st century, as clinical and epidemiological

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evidence mounted regarding its progressive potential. Driven by the global pandemics of obesity and type 2 diabetes mellitus, NAFLD has now unequivocally become the most prevalent chronic liver disease worldwide. Its clinical course is not indolent; advanced stages of the disease confer a significantly elevated risk for the development of cirrhosis, liver failure, and hepatocellular carcinoma [14, 15]. Moreover, it is fundamentally intertwined with systemic metabolic syndrome, engaging in a deleterious bidirectional relationship with conditions like type 2 diabetes and acting as an independent risk factor for cardiovascular, renal, and other extrahepatic morbidities [16].

The limitations inherent in the NAFLD framework, particularly its reliance on exclusionary criteria and its failure to explicitly acknowledge the central role of metabolic health, prompted a major re-evaluation. In 2020, a consensus statement from an international panel of experts proposed renaming the condition to metabolic dysfunction-associated fatty liver disease (MAFLD) [17]. This was more than a semantic change; it established positive, inclusive diagnostic criteria centered on the presence of metabolic dysfunction. Under this new paradigm, the diagnosis of MAFLD requires the demonstration of hepatic steatosis (by imaging, biomarkers, or histology) *plus* evidence of metabolic dysregulation, defined as overweight/obesity, the presence of type 2 diabetes, or the identification of at least two metabolic risk factors in lean individuals [18-20]. Critically, this definition allows for the co-existence of other liver diseases, such as viral hepatitis, autoimmune liver disease, acknowledging the reality of "multiple etiology" liver disease, which the old NAFLD criteria explicitly forbade [21]. This shift is comprehensively detailed in Table 1, which delineates the core differences between the NAFLD and MAFLD diagnostic approaches across several dimensions including naming strategy, diagnostic criteria, handling of co-existing liver diseases, recognition of lean individuals, risk stratification capacity, and implications for research and clinical practice. The table underscores how MAFLD moves from an exclusionary diagnosis to a positive one, enhances the identification of high-risk populations, and enables the study of more pathophysiologically homogenous patient groups.

Subsequently, in 2023, a multisociety Delphi consensus further refined the nomenclature to metabolic dysfunction-associated steatotic liver disease (MASLD), a change that broadens the conceptual umbrella and aligns terminology with the overarching theme of metabolic dysfunction driving steatosis [22]. This updated terminology continues to emphasize the metabolic core of the disease and importantly highlights metabolic risk even in individuals with normal body weight, a subgroup previously often overlooked in NAFLD guidelines. The move from NAFLD to MAFLD/MASLD thus integrates the metabolic underpinnings directly into the diagnostic framework, providing benchmarks that are embedded in the very risk factors that drive the disease.

Table 1. Comparison of NAFLD and MAFLD Core Differences.

Comparison Dimension	NAFLD	MAFLD
Naming strategy	Diagnosed after excluding alcohol and other liver diseases	Defined by metabolic dysfunction, may coexist with other liver diseases.
Diagnostic criteria	An exclusionary diagnosis based on hepatic steatosis (≥5%) after excluding other liver diseases	A positive diagnosis based on hepatic steatosis plus at least one of the following: overweight/obesity, type 2 diabetes, or the presence of at least two metabolic risk factors.
Co-existing Liver Diseases	Cannot co-exist. The diagnosis requires exclusion of other liver diseases, thus no "dual etiology" is recognized.	Can co-exist. MAFLD can overlap with other liver diseases, acknowledging and emphasizing "dual or multiple etiologies".
Recognition of lean steatosis	Often overlooked	Emphasized.
Risk stratification ability	Limited	Better identification of high-risk populations.
Research Implications	Heterogeneous study populations	More precise study populations.
Clinical adoption	Widely used but increasingly questioned	Gaining traction; aligns with precision medicine approaches

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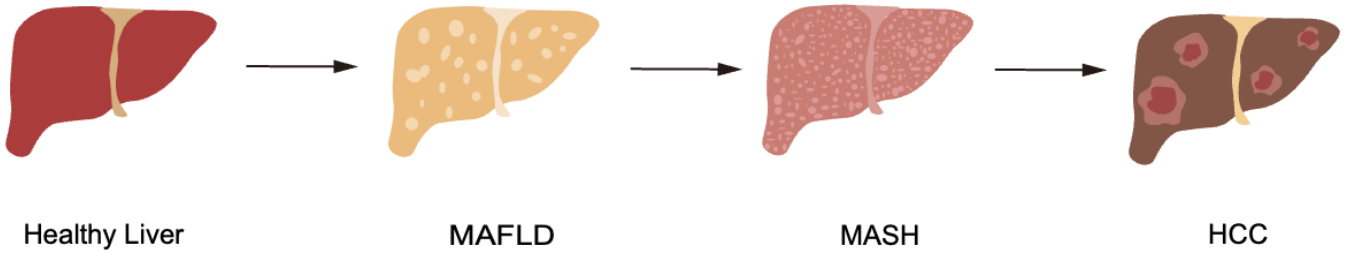


Fig. 1. This image illustrates the progression of liver disease from a healthy state to liver cancer. It begins with the Healthy Liver, depicted in red, representing a normal and healthy liver. The next stage is MAFLD, where fat accumulation appears in the liver, shown as yellow areas. Following that is MASH, where the liver undergoes more severe changes, including inflammation and fibrosis, represented by a mixture of red and yellow. Finally, the liver reaches the stage of HCC, where cancerous tumors develop, indicated by dark red areas with nodules. This progression highlights the path from a healthy liver to liver cancer.

The epidemiological impact of this diagnostic recalibration is substantial. MAFLD is now recognized as a leading cause of liver-related morbidity and mortality globally [18]. One of the key advantages of the MAFLD criteria is their enhanced ability to identify individuals with a high-risk phenotype for progressive liver disease. A systematic review by Ayada et al., encompassing 17 studies, confirmed that the prevalence of MAFLD is consistently higher than that of NAFLD when applied to the same populations, with rates frequently exceeding 30% in adults, reflecting the profound burden of metabolic disease worldwide [19]. The natural history of MAFLD is a dynamic and progressive process. It typically initiates with hepatic steatosis, defined as intracellular triglyceride content exceeding 5% of liver weight. This initial fat accumulation, driven by an imbalance between lipid acquisition (from circulating free fatty acids and de novo lipogenesis) and lipid disposal (via fatty acid oxidation and export as VLDL), sets the stage for subsequent liver injury. In a susceptible host, this steatotic environment can provoke hepatocyte stress, apoptosis, and the release of damage-associated molecular patterns, which in turn activate innate immune pathways and hepatic stellate cells. This cascade transforms simple steatosis into MASH, characterized by lobular inflammation, hepatocyte ballooning, and varying degrees of fibrosis. This inflammatory and pro-fibrotic milieu is the critical bridge from a reversible condition to advanced fibrosis, cirrhosis, and ultimately hepatocellular carcinoma in a significant subset of patients [17, 20].

Figure 1 is a conceptual illustration that effectively maps this disease progression. It begins with a healthy liver, depicted in a uniform color, transitioning to the MAFLD stage where discrete yellow foci symbolize the accumulation of fat droplets within hepatocytes. The subsequent MASH stage is represented by a intermixing of colors, indicating the addition of inflammatory infiltrates and early fibrotic changes to the underlying steatosis. The endpoint of hepatocellular carcinoma is shown as distinct, nodular dark masses arising within the liver architecture. This visual progression underscores the fact that MAFLD is not a static condition but a pathogenic continuum where early intervention is crucial to arrest or reverse its course.

2.2. Pathogenesis of MAFLD

The pathogenesis of MAFLD is complex and multifactorial, moving beyond earlier simplistic models to a nuanced understanding encapsulated by the "multiple-hit" hypothesis. While an oversupply of free fatty acids to the liver is a fundamental initiating event, the progression to steatohepatitis and fibrosis requires a constellation of parallel and interacting insults [17]. The central, reinforcing axis of this pathogenesis is the vicious cycle between insulin resistance and disordered lipid metabolism. Systemic insulin resistance, particularly in adipose tissue, leads to increased lipolysis and a sustained flood of free fatty acids into the portal circulation. Concurrently, hepatic insulin resistance promotes uncontrolled de novo lipogenesis even in the presence of high circulating lipids. The resultant lipid overload within hepatocytes, a state termed lipotoxicity, is the cornerstone of subsequent injury.

This lipid surplus has several deleterious consequences. It strains mitochondrial capacity for fatty acid β-oxidation, leading to incomplete oxidation, reactive oxygen species (ROS) overproduction, and oxidative stress. Furthermore, specific lipid species, such as free cholesterol and saturated fatty acids like palmitate, can directly induce endoplasmic reticulum (ER) stress and activate inflammatory pathways. The damaged and stressed hepatocytes release cytokines and danger signals that recruit immune cells, primarily pro-inflammatory macrophages, perpetuating a chronic inflammatory state within the liver. This milieu is further modulated by adipokines; adipose tissue dysfunction in obesity leads to an imbalance, with reduced levels of protective adiponectin and increased levels of pro-inflammatory leptin and resistin. Additionally, evidence strongly implicates gut dysbiosis, an alteration in the intestinal microbiota, in MAFLD pathogenesis. A "leaky gut"

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allows microbial products like lipopolysaccharide (LPS) to enter the portal circulation, where they activate toll-like receptor 4 (TLR4) on Kupffer cells and hepatocytes, further fueling hepatic inflammation and insulin resistance. Epigenetic modifications, influenced by diet and environment, and the role of innate immune sensors add further layers of complexity, making MAFLD a true paradigm of gene-environment interaction [17, 21]. This intricate network of interacting pathological mechanisms is schematically represented in Figure 2.

Figure 2 provides a systems-level overview of the multiple-hit hypothesis. It positions MAFLD at the center, surrounded by interconnected mechanistic spheres including lipotoxicity, adipokine imbalance, mitochondrial dysfunction, endoplasmic reticulum stress, oxidative stress, intestinal microbiota dysbiosis, epigenetic modifications, and inflammatory mediators. The visual interconnection of these elements powerfully conveys that no single pathway operates in isolation; rather, it is the synergistic and often synergistic crosstalk between metabolic disturbance, oxidative damage, inflammatory signaling, and environmental factors that drives disease progression from simple steatosis to steatohepatitis and fibrosis.

At the molecular level, the convergence of these hits often activates key stress-sensitive signaling cascades, such as the c-Jun N-terminal kinase (JNK) and inhibitor of nuclear factor kappa-B kinase (IKK)-NF-κB pathways. These pathways not only exacerbate local inflammation but also propagate insulin resistance by phosphorylating insulin receptor substrates on inhibitory serine residues, creating a feed-forward loop that amplifies the metabolic dysfunction. The culmination of chronic hepatocyte injury, death, and inflammation is the activation of hepatic stellate cells, the primary collagen-producing cells in the liver. Once activated, these cells proliferate and deposit excessive extracellular matrix, leading to the progressive fibrosis that determines long-term liver-related outcomes [21]. Therefore, the pathogenesis of MAFLD is a tapestry woven from threads of metabolic derangement, cellular stress, immune activation, and fibrogenic response.

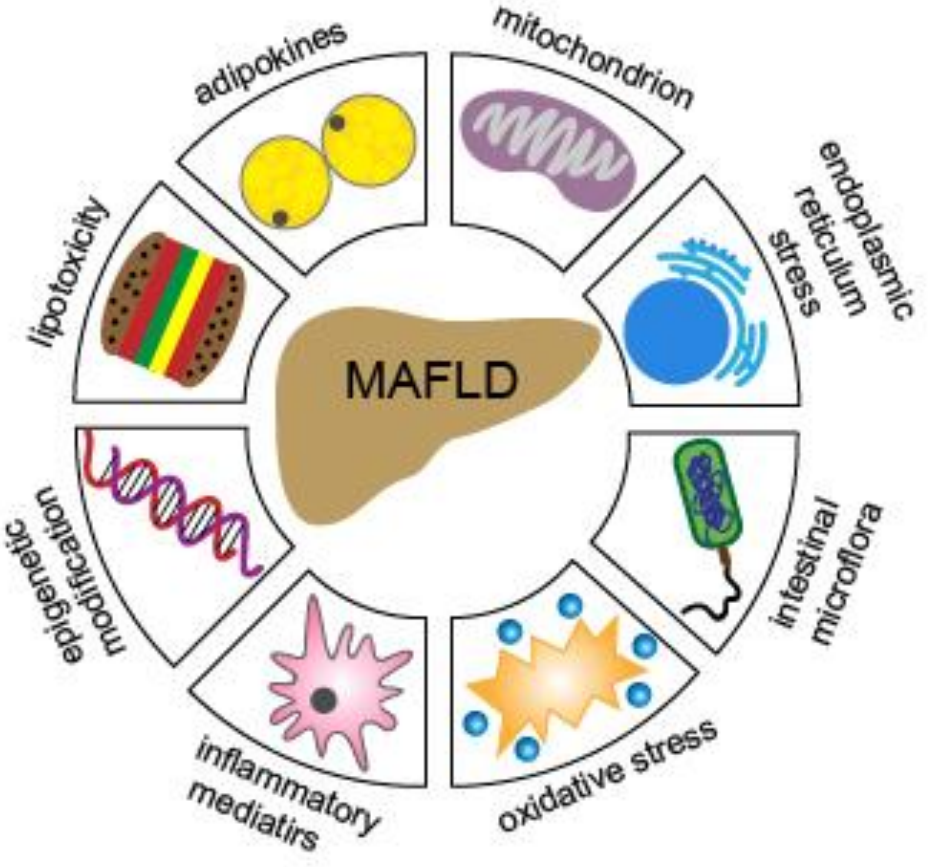


Fig. 2. This image illustrates various factors and mechanisms associated with MAFLD. The central focus is on MAFLD, with eight interconnected elements surrounding it, each representing a contributing factor or pathway involved in the disease. These include lipotoxicity, which refers to liver cell damage caused by excess fat accumulation; adipokines, signaling molecules released from fat cells that can influence metabolic functions; mitochondria, the energy-producing organelles, which may be impaired in MAFLD; and endoplasmic reticulum stress, which can disrupt normal cellular functions. Other factors include epigenetic modifications, which can alter gene expression, inflammatory mediators, which drive inflammation, oxidative stress, caused by an imbalance between free radicals and antioxidants, and intestinal microbiota, which plays a role in liver disease development. The image emphasizes how these mechanisms interact and contribute to the progression of MAFLD.

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2.3 Diagnosis of MAFLD

The diagnosis of MAFLD integrates the demonstration of hepatic steatosis with the confirmation of underlying metabolic dysfunction, a deliberate departure from the purely exclusion-based approach of NAFLD. The condition is clinically categorized into three main stages: metabolism-associated simple fatty liver (isolated steatosis), metabolism-associated steatohepatitis (MASH, featuring steatosis, inflammation, and hepatocyte injury with or without fibrosis), and MAFLD-associated cirrhosis. It is well-established that MASH is the stage most strongly associated with progression to clinically significant fibrosis, cirrhosis, and hepatocellular carcinoma [15].

The practical diagnostic algorithm, as refined by international consensus, follows a logical sequence [14, 22]. The first and foremost step is to confirm the presence of hepatic steatosis. This is typically achieved first through non-invasive imaging modalities. Abdominal ultrasonography is the most widely used initial test due to its accessibility, low cost, and reasonable sensitivity for detecting moderate-to-severe steatosis (typically >20-30% fat infiltration). Its limitations include operator dependence and reduced sensitivity in obese patients. Controlled Attenuation Parameter (CAP), measured via vibration-controlled transient elastography (FibroScan®), provides a quantitative estimate of steatosis and is increasingly used. Magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) is currently the most accurate non-invasive method for quantifying hepatic fat, serving as a non-invasive reference standard, though its cost and availability limit routine use. In cases of diagnostic uncertainty or to concurrently assess the histologic grade (activity of MASH) and stage (degree of fibrosis), a percutaneous liver biopsy remains the definitive diagnostic procedure. Histological analysis not only confirms steatosis but also identifies key features of MASH, hepatocyte ballooning, lobular inflammation, and precisely stages fibrosis, which is critical for prognosis and management decisions.

The second pillar of the MAFLD diagnosis is the positive identification of metabolic dysfunction, as per the consensus criteria [17]. This involves assessing the patient's metabolic phenotype. The criteria are met if the individual has either: 1) a body mass index (BMI) ≥ 25 kg/m² (or ≥23 kg/m² in Asian populations), 2) a pre-existing diagnosis of type 2 diabetes mellitus, or 3) in lean individuals (BMI < 25/<23 kg/m²), the presence of at least two of the following metabolic risk abnormalities: waist circumference ≥ 94 cm (men)/80 cm (women) (ethnicity-adjusted), blood pressure ≥ 130/85 mmHg or specific drug treatment, plasma triglycerides ≥ 150 mg/dL or specific drug treatment, plasma HDL-cholesterol < 40 mg/dL (men)/<50 mg/dL (women) or specific drug treatment, prediabetes (fasting glucose 100-125 mg/dL or HbA1c 5.7-6.4%), a homeostasis model assessment of insulin resistance (HOMA-IR) score ≥ 2.5, or a plasma high-sensitivity C-reactive protein level > 2 mg/L.

A critical and defining update in the MAFLD criteria is the deliberate move away from requiring the exclusion of other liver diseases or specific alcohol intake thresholds as a *condition for diagnosis*. While it remains essential clinical practice to evaluate for and quantify other potential contributors to liver disease (such as significant alcohol use, viral hepatitis, autoimmune conditions, or genetic disorders), their presence does not preclude a diagnosis of MAFLD. Instead, the diagnosis acknowledges the frequent reality of "dual etiology" liver disease. For instance, a patient with hepatitis C virus infection and significant metabolic risk factors would be diagnosed with both hepatitis C and MAFLD. This inclusive approach more accurately reflects real-world pathophysiology and ensures that the metabolic component of liver disease is recognized and potentially addressed, regardless of other co-existing conditions [22].

The diagnosis of MAFLD is established on a dual foundation: objective evidence of hepatic steatosis and concurrent evidence of metabolic dysregulation. This positive, inclusive framework facilitates earlier identification of at-risk individuals, encourages a holistic assessment of cardiometabolic health, and paves the way for targeted management strategies that address the root metabolic drivers of the disease, in conjunction with any other necessary liver-directed therapies.

3. PHARMACOLOGICAL MECHANISMS OF SILYMARIN

3.1. Silymarin: Composition and Pharmacological Properties

Silymarin is not a single molecular entity but rather a complex, standardized extract derived from the seeds and fruits of the milk thistle plant, *Silybum marianum* (L.) Gaertn. This extract is predominantly composed of a unique family of flavonolignans, which are biosynthetically derived from the coupling of a flavonoid precursor with coniferyl alcohol. The seeds of *Silybum marianum* are particularly rich in these bioactive compounds, with silymarin constituting their principal medicinal component, historically recognized for its therapeutic effects on hepatic and splenic disorders [23]. The pharmacological activity of silymarin is attributed to this specific mixture, with the major active constituents identified as silybin (also known as silibinin), isosilybin, silydianin, and silychristin. Among these, the diastereoisomeric pair silybin A and silybin B is the most abundant and pharmacologically significant, typically comprising 50-70% of a standardized silymarin extract [10]. The precise composition is critical, and modern pharmaceutical-grade silymarin is produced through standardized processes with quality rigorously controlled by analytical techniques such as high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GC-MS) fingerprinting, ensuring batch-to-batch consistency and validated biological activity in both in vitro and in vivo models [24].

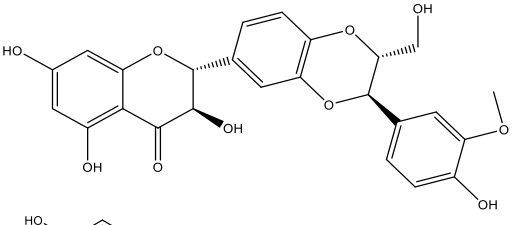
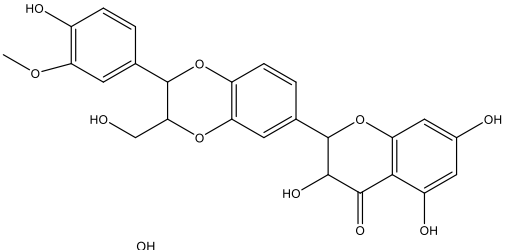
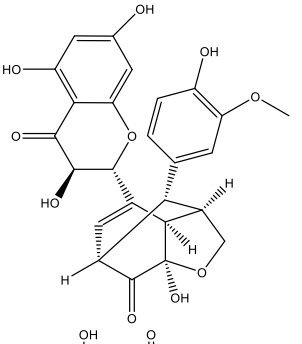
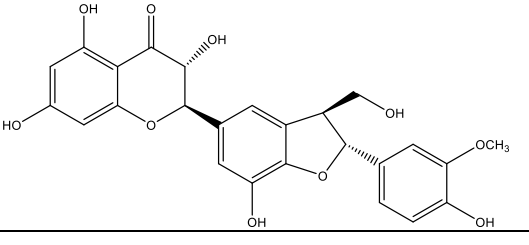
The structural characteristics of these key flavonolignans are detailed in Table 2, which presents the molecular formulas and structural diagrams for silybin,

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isosilybin, silydianin, and silychristin. A key feature unifying these compounds is their shared molecular formula (C~25~H~22~O~10~), yet each possesses a distinct stereochemical configuration and ring arrangement that influences its biological activity and metabolism. For instance, silybin and isosilybin are diastereomers, differing in the configuration at the C-10 and C-11 positions, which can affect their receptor binding and antioxidant potency. Silydianin and silychristin present different oxidative patterns and ring structures within the same flavonolignan scaffold. This table underscores that silymarin's therapeutic effect is likely the result of the combined, and potentially synergistic, action of these structurally related yet distinct molecules, rather than the effect of a single compound.

The hepatoprotective efficacy of silymarin arises from its multi-targeted engagement with diverse pathological pathways central to liver injury. A cornerstone of its mechanism is the potent anti-inflammatory action mediated through the suppression of the nuclear factor kappa-B (NF-κB) signaling pathway. By inhibiting the activation and nuclear translocation of NF-κB, silymarin downregulates the transcription of a wide array of pro-inflammatory cytokines and chemokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), thereby attenuating the chronic inflammatory milieu that drives hepatocyte injury and fibrosis [25, 26]. Concurrently, silymarin exhibits direct and indirect antioxidant properties. It can act as a free radical scavenger, directly neutralizing reactive oxygen species (ROS), and also inhibits the expression of inducible nitric oxide synthase (iNOS), reducing the production of potentially damaging nitric oxide (NO) radicals. Furthermore, silymarin is known to modulate cell membrane fluidity and stability, protecting hepatocytes from toxin-induced damage, and interestingly, it has been shown to bind to estrogen receptors, a mechanism implicated in its ability to stimulate hepatocyte regeneration [26]. These fundamental properties translate into a targeted therapeutic profile against the key pathological pillars of MAFLD. As illustrated in Figure 3, silymarin's benefits are multifaceted. The figure visually links the milk thistle plant to its derived compound and maps its primary therapeutic actions: potent antioxidant activity, hepatoprotection, anti-diabetic effects (via improving insulin sensitivity), and the promotion of mitochondrial health through processes like mitophagy.

Table 2. Structural characteristics of Silymarin.

Compounds	Structural formula	Structural characteristics
Silybin		$C_{25}H_{22}O_{10}$
Isosilybin		$C_{25}H_{22}O_{10}$
Silydianin		$C_{25}H_{22}O_{10}$
Silychristin		$C_{25}H_{22}O_{10}$

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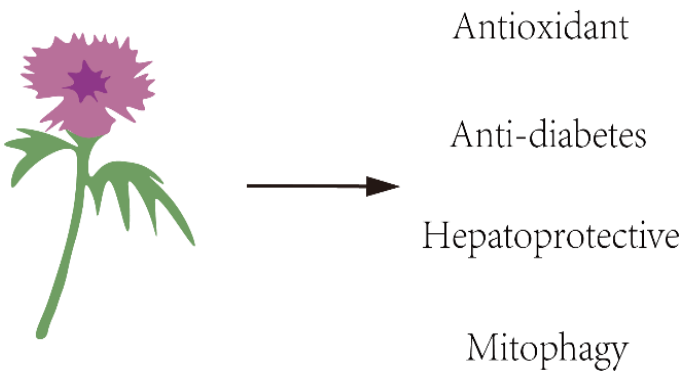


Fig. 3. This image highlights the potential health benefits of silymarin, a compound derived from the milk thistle plant. Silymarin is known for its antioxidant properties, helping to neutralize harmful free radicals in the body. It also has anti-diabetic effects, potentially improving insulin sensitivity and lowering blood sugar levels. Furthermore, silymarin is hepatoprotective, supporting liver health by preventing liver damage and promoting overall liver function. Additionally, it is involved in mitophagy, a process that helps remove damaged mitochondria, thus enhancing cellular health. The image visually links these therapeutic effects with the milk thistle plant.

This schematic effectively conveys that silymarin is not a single-pathway drug but a pleiotropic agent whose actions converge to protect the liver. By alleviating oxidative stress, improving insulin sensitivity, reducing de novo lipogenesis and promoting fatty acid oxidation, and stabilizing mitochondrial function, silymarin directly counteracts the core mechanisms driving MAFLD progression from steatosis to steatohepatitis [27]. Its mechanisms also extend to later disease stages, showing potential in modulating pathways involved in fibrogenesis and hepatocellular carcinoma development, positioning it as a candidate for managing the common end-stages of chronic liver disease.

3.2. Clinical Evidence of Silymarin in MAFLD Treatment

The transition from compelling mechanistic data to demonstrable clinical benefit is essential for any therapeutic agent. For silymarin, a growing body of clinical research supports its utility in managing MAFLD, primarily focusing on improvements in serum liver enzymes, lipid profiles, and radiological markers of steatosis. A persistent challenge in interpreting this literature is the variability in silymarin preparations used. Recognizing the inherent low oral bioavailability of native silymarin flavonolignans, clinical practice and research have increasingly focused on complexed formulations, such as silybin-phosphatidylcholine complexes or silybin bound with meglumine, designed to enhance solubility and absorption. Table 2, while primarily structural, implicitly highlights the chemical basis for these formulation efforts; by complexing these specific flavonolignan structures with phospholipids, their pharmacokinetic profile is favorably altered.

Early proof-of-concept studies established the biochemical efficacy of silymarin. For example, a controlled trial involving 64 MAFLD patients demonstrated that an 8-week regimen of 210 mg of silymarin per day led to statistically significant reductions in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels compared to placebo [28]. This finding was substantiated in larger and more comprehensive investigations. A three-month randomized study by Cheng and colleagues on 80 MAFLD patients compared a silymarin treatment group to a control group. The results revealed that the silymarin-treated cohort exhibited not only significant improvements in ALT and AST but also favorable reductions in total cholesterol, triglycerides, and key inflammatory cytokines including TNF-α, IL-8, and IL-18, linking biochemical improvement to a modulation of the underlying inflammatory state [29]. The scale of this effect is noteworthy; a meta-analysis encompassing data from 622 patients concluded that silymarin was significantly more effective than placebo in reducing elevated ALT levels, a cornerstone biomarker in liver disease monitoring [30].

Further studies have strengthened the evidence for specific silymarin formulations. Li et al. conducted a three-month trial comparing oral silybin capsules to the hepatoprotective agent thiopronin in 56 MAFLD patients. The silybin group achieved normalization of transaminases in 67% of patients, a rate significantly higher than the control group. Moreover, this group experienced pronounced reductions in cholesterol and triglycerides, and abdominal ultrasound assessment indicated a significant decrease in hepatic fat content, with overall treatment effectiveness reported above 90% [31]. The adjunctive role of silymarin has also been explored. In a study by Wang et al., patients receiving standard lipid-lowering therapy (atorvastatin) were randomized to receive either additional silybin capsules or not. The combination group demonstrated superior improvements in both ultrasound-assessed hepatic steatosis and serum lipid parameters after three months, suggesting that silymarin can provide additive benefit to conventional metabolic therapy [32].

Perhaps more compelling are studies assessing the impact of silymarin on disease progression, specifically liver fibrosis. A 48-week randomized trial involving 99 biopsy-proven MAFLD patients found that high-dose silymarin (700 mg three times daily) was associated with a reduction in histological fibrosis score, improvements in NAFLD Activity Score (NAS), and a decrease in the AST-to-Platelet Ratio Index (APRI), a non-invasive fibrosis marker, compared to placebo [33]. Although this trial was pioneering, its sample size underscores the need for larger confirmatory studies. This anti-fibrotic effect was also observed in a separate 24-week placebo-controlled trial in adults with MAFLD, including those with diabetes, where silymarin treatment led to measurable improvements in fibrosis markers [34].

The clinical potential of silymarin appears to be

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enhanced when used in combination therapy or in advanced delivery systems. Studies combining silymarin with statins like lovastatin have shown synergistic improvements in liver enzymes and lipids [35]. The combination of silymarin with vitamin E has yielded particularly interesting results. One study demonstrated that this combination not only improved insulin resistance but also induced positive changes in liver histology [36, 37]. This synergistic rationale led to the development of a sophisticated silymarin-vitamin E-phospholipid complex. In a pivotal multicenter, phase III trial involving 180 patients with histologically confirmed MAFLD, this complex (delivering 188 mg silymarin, 388 mg phosphatidylcholine, and 60 mg vitamin E daily) was administered for 12 months. The results were significant: normalization of aminotransferase levels, improvement in gamma-glutamyl transferase (GGT), reduction in ultrasound-determined steatosis grade, and beneficial effects on fasting glucose, insulin levels, and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index. Crucially, in a subset of 35 patients who underwent a follow-up liver biopsy, trends toward improvement in histological scores for steatosis, inflammation, ballooning, and fibrosis were observed [38-41]. This trial provides some of the strongest clinical evidence to date, linking a specifically formulated silymarin complex to improvements across a spectrum of metabolic, biochemical, and histological endpoints in MAFLD.

The long-term clinical use of silymarin across various liver conditions has generally affirmed its safety profile. It is well-tolerated, with a low risk of serious adverse events or significant drug-drug interactions [39]. The most commonly reported side effects are mild and gastrointestinal in nature (e.g., loose stools, nausea). In the controlled trials specific to MAFLD, no significant safety signals emerged, supporting its feasibility for potential long-term use in a chronic condition [38]. Collectively, the clinical evidence positions silymarin, particularly in bioavailable formulations, as an agent capable of exerting hypolipidemic and hepatoprotective effects through the modulation of hepatic lipid metabolism, suppression of inflammatory cascades, and improvement of systemic insulin sensitivity, as reflected in improved HOMA-IR and insulin tolerance test results [40, 41].

3.3. Antioxidant Effect of Silymarin

Oxidative stress is a pivotal pathogenic driver in MAFLD, resulting from an imbalance between the production of ROS and the cellular antioxidant defense capacity. Hepatocyte lipid overload leads to mitochondrial dysfunction and β-oxidation inefficiency, generating excess ROS which in turn peroxidize lipids, damage proteins and DNA, and activate pro-inflammatory and pro-fibrogenic pathways [42]. Silymarin confronts this oxidative assault through a multi-layered antioxidant strategy. Directly, the phenolic structure of its flavonolignans confers potent free radical scavenging (antioxidant) activity, effectively donating hydrogen atoms to neutralize ROS such as superoxide anion, hydroxyl radical, and peroxyl radicals, as demonstrated in various in vitro systems [43-45].

Beyond direct scavenging, silymarin exerts profound indirect antioxidant effects by bolstering the endogenous cellular defense system. A master regulator of this adaptive response is the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2). Under oxidative stress, NRF2 translocates to the nucleus and binds to the Antioxidant Response Element (ARE), activating the transcription of a battery of cytoprotective genes encoding enzymes like heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), and glutathione S-transferases (GSTs). Silymarin has been shown to upregulate NRF2 expression and promote its nuclear translocation. In a high-fat diet-induced rat model of MAFLD, silymarin treatment effectively promoted NRF2 activation [46-50], a finding replicated in vitro in HepG2 cells, where silymarin-induced antioxidant effects were mediated via the NRF2 pathway [51]. This activation of the NRF2-ARE axis represents a powerful, sustained mechanism to enhance the liver's intrinsic resistance to oxidative damage.

Silymarin's antioxidant protection extends to the organellar level, specifically safeguarding mitochondria, both the primary source and a major target of ROS in MAFLD. It ameliorates lipid accumulation by preserving the integrity and function of the mitochondrial respiratory chain complexes in steatotic hepatocytes [46]. Furthermore, silymarin helps maintain mitochondrial membrane fluidity and stability, preserves mitochondrial membrane potential ($\Delta\Psi m$), and supports efficient oxidative phosphorylation, thereby protecting mitochondrial energetics in the face of metabolic stress [47, 48]. Recent research has also linked silymarin to the activation of sirtuin 1 (SIRT1), a NAD+-dependent deacetylase involved in cellular stress response and metabolism. A study found that silymarin restored cellular NAD+ levels and induced the SIRT1/AMP-activated protein kinase (AMPK) pathway in a MAFLD model, a pathway crucial for promoting mitochondrial biogenesis, fatty acid oxidation, and mitigating oxidative stress [52, 53]. Through this combination of direct scavenging, NRF2-mediated gene induction, and mitochondrial stabilization, silymarin comprehensively mitigates the oxidative stress that is central to MAFLD pathogenesis.

3.4 Anti-inflammatory Effects of Silymarin

Chronic low-grade inflammation is the critical link between simple hepatic steatosis and the progressive injury characteristic of MASH. Silymarin potently modulates multiple nodes within the hepatic inflammatory network. Its most characterized anti-inflammatory mechanism is the inhibition of the NF-κB pathway, as previously mentioned. In experimental models of non-alcoholic steatohepatitis, silymarin treatment has been shown to significantly reduce the DNA-binding activity of key NF-κB subunits, p65 and p50, thereby dampening the transcriptional output of this central inflammatory switch [54, 55].

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Emerging research reveals that silymarin's anti-inflammatory actions are more extensive. In a high-fat diet-induced mouse model, silymarin was found to modulate bile acid metabolism, specifically increasing the levels of 7-ketodeoxycholic acid (7-KDCA). This bile acid derivative then acts as a signaling molecule, simultaneously activating the Farnesoid X Receptor (FXR), which has anti-inflammatory and metabolic regulatory roles, and inhibiting Toll-like Receptor 4 (TLR4) signaling, a key pathway for pro-inflammatory cytokine production in response to gut-derived endotoxins like lipopolysaccharide. This dual modulation of FXR and TLR4 contributes significantly to silymarin's ability to alleviate lipid deposition and inflammation in the liver [56]. Furthermore, silymarin exhibits immunomodulatory properties beyond innate immunity. It has been shown to inhibit the proliferation of T-lymphocytes, key adaptive immune cells, by interfering with the activation of the Mitogen-Activated Protein Kinase (MAPK) signaling pathway (including ERK, JNK, and p38), which is essential for T-cell activation and cytokine production [57]. This broad-spectrum suppression of both innate (via NF-κB, TLR4) and adaptive (via T-cell modulation) immune responses underpins silymarin's potent anti-inflammatory efficacy in the complex inflammatory milieu of MAFLD.

3.5. Anti-fibrotic Effects of Silymarin

The progression from MASH to cirrhosis is defined by the accumulation of extracellular matrix, or fibrosis. Hepatic stellate cells (HSCs) are the principal effector cells responsible for fibrosis; upon activation by inflammatory and oxidative signals, they transdifferentiate into proliferative, contractile, collagen-producing myofibroblasts [58]. The antifibrotic effect of silymarin in chronic liver disease is closely associated with the suppression of HSC activation. In vitro studies on human HSCs have demonstrated that silymarin, and its major constituent silybin, exert direct anti-fibrogenic effects by reducing HSC proliferation, inducing cell cycle arrest, and promoting apoptosis in activated HSCs. They also downregulate the expression of key fibrogenic markers, including alpha-smooth muscle actin (α-SMA) and type I procollagen [59]. These in vitro findings are supported by in vivo evidence. In a dietary rat model of NASH, silymarin treatment significantly inhibited hepatic fibrosis, an effect correlated with a marked reduction in the number of α-SMA-positive activated HSCs and decreased levels of procollagen mRNA in liver tissue [60]. By targeting the central cellular mediator of fibrosis, silymarin interferes with a critical late step in MAFLD progression, offering potential to prevent or slow the advancement to cirrhosis.

3.6. Other Metabolic and Regulatory Effects of Silymarin

The therapeutic reach of silymarin in MAFLD extends into finer metabolic and cellular stress adjustments. Metabolomic studies in MASH mouse models indicate that silymarin treatment induces significant alterations in amino acid and lipid metabolism profiles, correcting some of the metabolic disturbances associated with the disease [61]. Its lipid-modulating effects are robust; in high-fat diet-fed mice, silymarin administration significantly counteracts diet-induced alterations in hepatic lipid metabolism, reducing overall hepatic triglyceride and cholesterol content [62].

A crucial pathway through which silymarin improves metabolic parameters is by ameliorating endoplasmic reticulum (ER) stress. Lipid overload and oxidative stress can disrupt ER function, triggering the Unfolded Protein Response (UPR), which exacerbates insulin resistance and apoptosis. Silymarin has been shown to alleviate ER stress in hepatocytes. This action is linked to its ability to target the insulin receptor substrate-1 (IRS-1)/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway. In models of insulin resistance induced by palmitate or high-fat diet, silymarin enhances insulin signaling by promoting the tyrosine phosphorylation of IRS-1 (necessary for signal propagation) and inhibiting its inhibitory serine phosphorylation, thereby restoring the PI3K/Akt pathway activity. This leads to improved glucose uptake and decreased hepatic gluconeogenesis, ameliorating both steatosis and insulin resistance [63, 64]. It is noteworthy that the activation of stress kinases like c-Jun N-terminal kinase (JNK), which is inhibited by silymarin, is a common mediator linking lipid toxicity, ER stress, and insulin resistance, suggesting interconnected mechanisms.

The improvement of MAFLD by silymarin is characterized by its simultaneous engagement of a diverse array of therapeutic targets implicated in the disease's onset and progression. From mitigating the initial metabolic insults of oxidative stress and insulin resistance to quelling the consequential inflammatory response and finally inhibiting the fibrotic scarring that leads to organ failure, silymarin acts as a multi-target therapeutic agent. Considering the chronic nature of MAFLD requiring long-term management, silymarin's historical use, high safety profile, and pleiotropic mechanism of action position it as one of the most promising natural compounds for inclusion in comprehensive treatment strategies for this pervasive metabolic liver disorder.

4. CONCLUSION

The accumulated body of research underscores silymarin as a compelling candidate for the management of metabolic dysfunction-associated fatty liver disease. Its pleiotropic mechanisms, spanning antioxidant, anti-inflammatory, anti-fibrotic, and metabolic regulatory pathways, allow it to target multiple facets of MAFLD pathogenesis. Clinically, silymarin, especially in formulations designed to overcome its inherent bioavailability limitations, has demonstrated meaningful improvements in biochemical, imaging, and histological endpoints. Notably, combination therapies incorporating silymarin with vitamin E or conventional lipid-lowering agents have shown synergistic potential,

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highlighting its role within a multifaceted treatment strategy. However, several challenges must be addressed to translate this promise into widespread clinical practice. The variability in silymarin preparation, dosage, and study design across trials complicates direct comparisons and consensus on optimal protocols. Future research must prioritize large-scale, randomized controlled trials with standardized outcome measures, prolonged follow-up, and well-defined patient stratification, particularly considering the heterogeneous nature of MAFLD and its frequent coexistence with other liver conditions. Additionally, further pharmacodynamic and pharmacokinetic studies are needed to refine delivery systems that enhance absorption and liver-targeted distribution. While silymarin is not a standalone cure, its favorable safety profile and multi-mechanistic action support its integration as a valuable component in the therapeutic arsenal against MAFLD. With continued rigorous investigation, silymarin has the potential to become a well-established, evidence-based adjunct in the effort to mitigate the progression of this prevalent metabolic liver disorder.

5. FUTURE DIRECTIONS

Future research on silymarin for metabolic dysfunction-associated fatty liver disease (MAFLD) should pursue a multi-faceted and rigorous pathway to solidify its role in clinical hepatology. A primary and immediate direction involves the design and execution of large-scale, multicenter, randomized controlled trials with extended follow-up periods. Current evidence, while promising, often stems from studies with limited sample sizes, heterogeneous patient populations, and variable formulations of silymarin. Definitive phase III trials are needed that employ standardized, high-bioavailability silymarin complexes, use histological endpoints, such as improvement in fibrosis stage or MASH resolution, as primary outcomes, and directly compare silymarin against first-line lifestyle interventions and emerging pharmacotherapies. These trials must also rigorously assess long-term safety and hard clinical outcomes, including progression to cirrhosis and liver-related mortality.

Concurrently, deeper translational investigation into the precise molecular mechanisms of silymarin is warranted. Much of the understood pharmacology revolves around broad pathways like NF-κB inhibition and NRF2 activation. Future work should employ advanced omics technologies, including transcriptomics, proteomics, and metabolomics, in well-characterized preclinical models and human biopsy samples to map the specific gene networks, protein interactions, and metabolic fluxes modulated by silymarin and its constituents. This will clarify whether the observed clinical benefits are driven primarily by silybin or result from synergistic activity among flavonolignans, and will help identify predictive biomarkers of treatment response.

Overcoming the pharmacokinetic limitations of silymarin remains a crucial engineering challenge. Research must continue to innovate novel drug delivery systems, such as advanced nanoparticle formulations, phospholipid complexes, and conjugates designed to enhance solubility, gastrointestinal stability, and targeted hepatic uptake. Exploring pro-drug strategies or synthesizing novel analogs with improved pharmacokinetic profiles while retaining the beneficial multi-target activity could yield next-generation compounds.

Furthermore, the therapeutic potential of silymarin within personalized medicine frameworks for MAFLD deserves exploration. Given the disease's heterogeneity, future studies should investigate whether specific patient subgroups, defined by genetic polymorphisms, gut microbiota signatures, or metabolic phenotype, derive exceptional benefit from silymarin therapy. This stratified approach could optimize treatment efficacy and resource allocation.

Finally, the role of silymarin in combination regimens requires systematic evaluation. Synergistic studies with other hepatoprotective agents, antidiabetic drugs like GLP-1 receptor agonists, or antifibrotics should be prioritized. Understanding these pharmacodynamic interactions will inform rational polytherapy protocols for advanced disease. In parallel, robust real-world evidence studies and pharmacovigilance programs are essential to confirm the effectiveness and safety of silymarin across diverse, unselected patient populations in routine clinical practice, complementing data from controlled trials.

The future of silymarin research lies in transitioning from proving general efficacy to defining precise mechanisms, optimal delivery, predictive biomarkers, and its ideal place within evolving MAFLD treatment algorithms through a combination of rigorous basic science and structured clinical investigation.

DECLARATIONS

Ethical Approval

We affirm that this manuscript is an original work, has not been previously published, and is not currently under consideration for publication in any other journal or conference proceedings. All authors have reviewed and approved the manuscript, and the order of authorship has been mutually agreed upon.

Availability of data and material

All of the data obtained or analyzed during this study is included in the report that was submitted.

Conflicts of Interest

The authors declare that they have no financial or personal interests that could have influenced the research and findings presented in this paper. The authors alone are responsible for

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the content and writing of this article.

Authors' contributions

All authors contributed equally to this work.

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