

A Comparative Study on the Mechanisms and Therapeutic Efficacy of Common Natural Products and Their Derivatives in the Treating Metabolic Dysfunction Associated Steatohepatitis

Yuhang Liu^{1, a}

¹School of Biotechnology and Food Engineering, Hefei University of Technology, Hefei, China

^a2023213599@mail.hfut.edu.cn

Abstract

MASH is a chronic liver disease with high global prevalence, which has become a major driver of cirrhosis and liver cancer. This study addresses the limitation that most existing research focuses on individual compounds, so four natural products, which are curcumin, silybin, tanshinone IIA, and Lycium barbarum polysaccharide (LBP), were selected based on their extensive documentation and structural diversity. The main goal was to systematically compare their mechanisms of action and clinical effectiveness against MASH. Peer-reviewed articles published between 2020 and 2026 were systematically retrieved and screened according to predefined quality criteria to build an evaluation framework. Then, the analysis examined four main areas: lipid regulation, anti-inflammation, antioxidant activity, and anti-fibrosis work. Data synthesis was performed through systematic cross-comparison of included studies. The results show that the curcumin phospholipid complex called Meriva is the most promising candidate. We put forward a few different combination treatment plans because their individual ways of working might complement each other and make the total effect better than any single one. By doing all of this work, it fills a gap that existed in past systematic studies of natural products for MASH and a scientific basis for precision medicine and drug development is provided.

Keywords

Metabolic dysfunction associated steatohepatitis; MASH; natural products; derivatives.

1. INTRODUCTION

MASH, formerly known as non-alcoholic steatohepatitis (NASH), is known for having steatosis in the liver, inflammatory infiltration, and fibrosis. More than 30% of people have this condition, and it poses a significant threat to public health. Insulin resistance, oxidative stress, and an unbalanced gut microbiota all exacerbate its progression over time. Right now, most treatments are just about changing people's daily habits. Clinical tests done with man-made drugs have not gotten very good results, this may be attributed to the limited targeting of single signaling pathways by these agents. Natural products, though, have special benefits when treating metabolic problems. This is because they have so many different structures, and they can start multiple working mechanisms at the same time.

What do these mechanistic differences mean for treatment? In practice, they imply variations in therapeutic effect and potential for drug development. However, most studies still focus on individual compounds, either to validate their activity or to explore their derivatives. Systematic comparisons between several well-studied natural products are conspicuous by their absence, leaving clinical decisions and drug discoveries without sufficient evidence.

To tackle this gap, we selected four classes of commonly investigated natural products with diverse chemical structures. We quantitatively compared their therapeutic differences, analyzed mechanism-specific features, and built a multidimensional evaluation system. This allowed us to screen optimal drug candidates and rationally propose combination regimens, supplying a scientific basis for precision treatment and drug development in MASH.

2. RESEARCH METHODS AND LITERATURE SCREENING

2.1. Literature Search Strategy

A computerized search was conducted in the PubMed, Web of Science, Scopus, and CNKI databases, covering the period from January 1, 2020 to March 19, 2026. Search terms included “natural products,” “curcumin,” “silybin,” “tanshinone IIA,” “Lycium barbarum polysaccharide (LBP),” and “MASH.”

2.2. Inclusion and Exclusion Criteria

Include studies that follow standardized research designs and provide data on pharmacological effects; exclude duplicate, incomplete, and low-quality studies. The study subjects must be animal models, and the interventions must consist of single or compound natural products. Mechanism studies must explicitly involve MASH biomarkers and signaling pathways such as TGF- β , PPARs, and FXR. Include journal articles and master’s and doctoral theses; exclude purely textual reports, commentaries, and reviews.

3. DIFFERENCES IN THE MECHANISMS BY WHICH COMMON NATURAL PRODUCTS AND THEIR DERIVATIVES COMBAT MASH

3.1. Mechanisms of Lipid Metabolism Regulation

Curcumin-phospholipid complex activates AMPK α /PPAR α to promote fatty acid β -oxidation and suppresses SREBP-1c, lowering hepatic triglycerides [1-3]. Sodium tanshinone IIA sulfonate directly inhibits SREBP-1c, FAS, and ACC1, reducing lipid droplets in HepG2 cells [4-5]. LBP-Se boosts SCFA-producing bacteria like Bifidobacterium and Lactobacillus, activating AMPK via the gut-liver axis and suppressing lipid synthesis [6-7]. Silybin-phospholipid complex inhibits DGAT1 to cut triglyceride synthesis and enhances apoB-mediated VLDL secretion for lipid export [8-10].

3.2. Anti-inflammatory Mechanisms

Curcumin derivative C66 binds MD2 to block TLR4/NF- κ B, preventing NLRP3 inflammasome assembly and IL-1 β maturation [3, 11]. Tanshinone IIA dampens inflammation by reducing HSC-derived IL-17 and Th17 cell recruitment [12]. Additional anti-inflammatory effects of curcumin involve the inhibition of the PI3K/Akt/HIF-1 α pathway in MASH [13]. LBP strengthen the intestinal barrier, limiting endotoxin translocation and the downstream TLR4-mediated inflammatory cascade [6]. The silybin derivative SLB-D1 activates Nrf2 to suppress ROS, which in turn inhibits NF- κ B nuclear translocation and the expression of pro-inflammatory factors [8, 14].

3.3. Antioxidant Mechanisms

Curcumin derivatives scavenge ROS and inhibit NOX4 activity [1, 15]. LBP maintain redox balance by increasing intracellular GSH levels [6]. Through activation of the Nrf2/HO-1 pathway, silybin derivatives upregulate antioxidant enzymes such as SOD and GSH-Px and scavenge ROS [8]. Tanshinone IIA has also been shown to reduce oxidative stress via activating the PPAR α /FGF21 axis [6].

3.4. Anti-fibrotic Mechanisms

By acting on NF- κ B and TGF- β 1 pathways, curcumin derivatives suppress HSC activation [1, 3, 16].

Tanshinone IIA blocks HSC proliferation and migration—this occurs through PDGF-BB/PDGFR β [12, 17].

LBP shows a weaker direct anti-fibrotic effect. Instead, it acts mainly through gut microbiota modulation [6].

The silybin-phospholipid complex reduces collagen deposition. It does so by inhibiting TGF- β 1/Smad3 and CTGF [8, 18].

4. COMPARISON OF TREATMENT EFFICACY

4.1. Improvement in Hepatic Lipid Metabolism

In a 72-week study, Meriva was evaluated in 52 patients with biopsy-confirmed non-alcoholic fatty liver disease (NAFLD). Triglycerides fell by 36 mg/dl and LDL cholesterol by 39 mg/dl. HDL cholesterol increased by 10 mg/dl [19]. Another study was a 12-month randomised controlled trial involving 227 overweight patients with type 2 diabetes. Curcumin (1,500 mg/day) significantly reduced hepatic steatosis (HFC) and liver stiffness [3]. In rats with acute hepatic steatosis (MASH) induced by an MCD diet, curcumin reduced hepatic triglycerides by approximately 42% [20].

Silybin, tested in an HFHC-induced MASH model, inhibited weight gain, reduced serum lipids, improved hepatic steatosis, and alleviated lipotoxicity by modulating C16:1 and PUFA levels [21-22].

Tanshinone IIA suppressed SREBP-1c, FAS, and ACC1, reducing PA/OA-induced lipid droplet accumulation in HepG2 cells [6, 23-24].

When combined with aerobic exercise, LBP activated the AMPK/PPAR α /PGC-1 α pathway in HFD-fed MASH rats, promoting mitochondrial biogenesis and fatty acid oxidation [13, 25].

4.2. Inhibition of Inflammatory Factors

In a 72-week clinical trial of 52 biopsy-confirmed NASH patients, Meriva cut triglycerides by 36 mg/dl, LDL cholesterol by 39 mg/dl, and raised HDL by 10 mg/dl [19]. Another 12-month randomized controlled trial gave 1500 mg curcumin daily to 227 overweight type 2 diabetes patients, leading to clear drops in liver fat content (CAP) and liver stiffness [3]. And in MCD-induced MASH mice, curcumin lowered liver triglycerides by about 42% [20].

Tanshinone I disrupted the NLRP3-ASC interaction, specifically inhibiting NLRP3 activation and reducing IL-1 β /IL-18 release [18, 26]. Tanshinone IIA dampened inflammation by limiting HSC-derived IL-17 and Th17 cell recruitment [23].

Silybin derivatives activate Nrf2 to suppress ROS, thereby inhibiting NF- κ B nuclear translocation [27], furthermore, silybin blocks NLRP3 inflammasome assembly via the NAD⁺/SIRT2 pathway [28].

LBP enhanced intestinal barrier integrity, reducing endotoxin translocation and TLR4-mediated cascades [29].

4.3. Improvement of Fibrosis

Curcumin derivatives inhibited NF- κ B/TGF- β 1 crosstalk and HSC activation [20]. In a 72-week trial, Meriva led to ≥ 1 stage fibrosis improvement in 50% of patients versus 8% on placebo (RR=6.50), and $\geq F2$ stage reversal in 42% versus 0% (RR=18.01) [19].

Silybin, for its part, suppressed hepatocyte succinate production and secretion, blocking the succinate/GPR91 axis to reverse HSC activation and fibrosis [17, 30].

Tanshinone IIA blocked HSC proliferation and migration via PDGF-BB/PDGFR β [23], and prevented fibrosis by regulating NET formation and hepatocyte apoptosis [31].

4.4. Regulation of Liver Enzyme Levels

A meta-analysis showed silybin/silymarin significantly reduced ALT (WMD: -7.36 U/L) and AST (WMD: -6.03 U/L) in NAFLD/MASH patients [32]. A 12-month regimen combining silybin-phospholipid complex with vitamin E significantly improved liver enzyme levels and histology in MASH patients [33-34].

Table 1. A Comparative Analysis of the Efficacy of Four Natural Products in Treating MASH

Evaluation Criteria	Curcumin	Silybin	Tanshinone IIA	LBP
Improved liver lipid metabolism	Strong [2-3, 19] (TG $\downarrow$ 36mg/dL LDL-C $\downarrow$ 39mg/dL)	Moderate [21-22] (TC/TG/LDL-C $\downarrow$)	Moderate [4-5, 24] (Inhibits SREBP-1c)	Weak [6m 13, 25] (Regulating gut-liver axis)
Inhibition of inflammatory factors	Strong [3, 19, 35] (Inhibits NF- κ B TNF- α /IL-6 $\downarrow$)	Moderate [8, 14, 27] (Activate Nrf2 Inhibits NF- κ B)	Strong [12, 18, 26] (Inhibits NLRP3 Block IL-17)	Weak [6, 29] (Strengthens intestinal barrier)
Improvement in fibrosis	Strong [19-20] (50% fibrosis improvement 62% MASH resolution)	Moderate [8, 17, 30] (Inhibits HSC activation Reduces collagen deposition)	Strong [12, 23, 31] (Inhibits PDGF-BB Blocks HSC migration)	Weak [6, 29, 36] (Indirect anti-fibrotic effect)
Regulation of liver enzyme levels	Moderate [2, 19] (ALT/AST $\downarrow$)	Strong [32-33] (ALT $\downarrow$ 7.36 U/L AST $\downarrow$ 6.03 U/L)	Moderate [5, 23] (ALT/AST $\downarrow$)	Weak [13, 29] (Minor improvement)

5. PHARMACOLOGICAL AND SAFETY EVALUATION

5.1. Pharmacokinetic Characteristics

Standard curcumin has low oral bioavailability, but the phospholipid complex Meriva enhances it about sevenfold [19]. Nicotinoyl curcumin boosts absorption through better water solubility and membrane permeability [37-38]. Silybin also suffers from poor bioavailability; its phospholipid complex gives around fourfold greater exposure [33]. Tanshinone IIA has poor water solubility, while its sodium sulfonate derivative offers better formulation characteristics [23]. LBP are water-soluble macromolecules with restricted gut uptake, so they primarily work via gut microbiota modulation [29]. Research into nanoformulations of LBP is ongoing [39].

5.2. Safety Comparison

A 72-week trial in 52 MASH patients reported that Meriva's adverse events were rare, mild, and comparable to placebo [19]. Meriva also holds FDA GRAS status [2, 40]. A meta-analysis showed no significant difference in adverse reaction rates between silybin and controls [32]. Mild nausea, diarrhea, and headache occurred in under 5% of patients [33]. For sodium

tanshinone IIA sulfonate injection, adverse effects such as rash, itching, and dizziness have an incidence below 3% [23]. Long-term oral LBP, a traditional food medicine, shows no notable toxic effects [29, 41].

Table 2. Comparison of Medicinal Properties and Safety of Four Natural Products

Evaluation Criteria	Curcumin	Silybin	Tanshinone IIA	LBP
Bioavailability	Moderate [2, 19] (7-fold increase in phospholipid complexes)	Medium [8, 23] (4-fold increase in phospholipid complex)	Low to moderate [23] (Sodium sulfonate injection improves solubility)	Low [29, 39] (Not absorbed by the intestines)
Formulation Development	High [9, 19, 40] (Market formulation Meriva available)	High [32-33] (Market formulation Legalon SIL available)	Moderate [23] (Injection available)	Low [29, 36, 41] (Health Supplements or Compound Formulations)
Adverse reactions	Rare [2, 19, 40] (Mild gastrointestinal reactions)	Rare [32-33] ($<5\%$, nausea and diarrhea)	Rare [23] ($<3\%$, rash and dizziness)	Rare [29, 41] (Long-term safety)
Clinical evidence	High [2-3, 19] (Phase III clinical trial)	High [32-33] (Multiple RCTs and Meta-analyses)	Low [18, 23, 26, 31] (Preclinical or Small-scale)	Low [13, 25, 29, 36] (Preclinical research)

6. MULTIDIMENSIONAL ASSESSMENT AND COMBINATION THERAPY RECOMMENDATIONS

6.1. Multidimensional Ranking

We evaluated the four natural products against four criteria: scope of mechanisms of action, efficacy, pharmacological potential and safety. Meriva, which is the curcumin and phospholipid complex, achieved the highest overall score. Its mechanisms of action cover lipid metabolism, inflammation, oxidative stress and fibrosis. Clinical data confirm that Meriva achieved a 62% resolution rate for MASH, compared with 12% for the placebo [19-20]. A commercially available formulation and excellent safety further enhance its profile [9, 35, 40].

The silybin-phospholipid complex came second. Legalon SIL, its European-approved formulation, has a robust safety record as an adjunctive liver therapy [32]. Silybin not only exerts antioxidant and anti-inflammatory effects but can also reverse fibrosis. It does so by blocking succinate/GPR91 [17, 30] and inhibiting NLRP3 assembly through NAD⁺/SIRT2 [28]. Its clinical potency, however, lags somewhat behind that of Meriva [21, 27, 32].

Tanshinone IIA exhibits powerful anti-fibrotic and anti-inflammatory actions. Poor water solubility and a shortage of large-scale clinical data, however, limit its development potential

[18, 23, 26, 31]. *Lycium barbarum* polysaccharides bring a distinctive gut-liver axis mechanism, yet show relatively weak anti-fibrotic efficacy overall [13, 29, 36, 39]

6.2. Combination Therapy Regimens

The compounds act via distinct pathways, giving three combinations. Pair curcumin with silybin: curcumin suppresses NF- κ B and activates AMPK, while silybin engages Nrf2 and blocks succinate/GPR91 [17, 30]. Together they yield synergistic anti-inflammatory and antioxidant effects. In a clinical report, adding silybin to Jianspi Jiangzhi Decoction raised the response rate to 92.50%. That was above the 75.00% for silybin alone [34].

Curcumin and LBP act on both the liver and the gut. Whilst curcumin acts via hepatic pathways, LBP strengthens the intestinal barrier and regulates the gut microbiota via the gut-liver axis [29]. The synergistic action of these two compounds inhibits the entry of endotoxins, enhances the anti-inflammatory effects of curcumin, and produces a coordinated effect [7, 41].

Silybin combined with tanshinone IIA has antioxidant, hepatoprotective, anti-inflammatory, and anti-fibrotic properties. Silybin eases oxidative stress and hepatocyte injury. Tanshinone IIA suppresses HSC activation [23] and the NLRP3 inflammasome [18, 26]. This pairing tackles multiple pathological steps in MASH, slowing collagen deposition and progression toward cirrhosis.

7. CONCLUSION

This investigation investigated the four natural products curcumin, silybin, tanshinone IIA and LBP, as well as their derivatives, in the treatment of Metabolic dysfunction-Associated Steatohepatitis (MASH). The aim was to explore their action mechanisms and therapeutic effects. Each substance has its own specific target and metabolic pathway. Curcumin mainly inhibits NF- κ B and activates AMPK/PPAR α , but silybin depends on the activation of Nrf2/HO-1. Tanshinone IIA affects the NLRP3 inflammasome and PDGF-BB/PDGFR β pathway, while LBP regulates the gut microflora and the relationship between gut and liver. A comprehensive assessment showed that Meriva is the most promising candidate. This curcumin-phospholipid complex has many functions, high efficiency, good pharmacological properties and safety. Some combined therapies are also suggested because of the complementary mechanisms. They include curcumin combined with silybin, curcumin combined with LBP, and silybin combined with tanshinone IIA. These combinations may be beneficial for personalized treatment. The research has connected the systematic comparison of natural products in the treatment of MASH, and it has expanded the multifunctional mechanism framework and promoted drug development. Nevertheless, some issues exist. For example, the Meriva trial involved only 52 patients [19], which may affect the reliability. Moreover, we have not considered the combination of natural products with synthetic drugs. In the future, further research should be conducted based on larger scale trials and examine the treatment with agents like FXR agonists. Structure-activity studies on the derivatives can enhance the pharmacological value and specific targets.

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