Drug Design, Development and Therapy

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REVIEW

The Active Components of Traditional Chinese Medicines Regulate the Multi-Target Signaling Pathways of Metabolic Dysfunction-Associated Fatty Liver Disease

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Abstract: Metabolic dysfunction-associated fatty liver disease (MAFLD), which is characterized by hepatocyte lipid accumulation driven by systemic metabolic dysregulation, represents a critical therapeutic challenge in the context of the global metabolic syndrome epidemic. The clinically recommended drugs for MAFLD mainly include antioxidants, hepatoprotective anti-inflammatory drugs, and weight-loss drugs. However, the mechanisms underlying the progression of MAFLD is characterized by nonlinearity, highlighting the urgent need for safer multi-target alternative therapies. Although existing single-target pharmacological interventions often show limited efficacy and adverse effects, the multi-component and multi-target nature of the active ingredients in traditional Chinese medicine (TCM) formulations represent new opportunities for systemic metabolic regulation. In this study, by searching PubMed and Web of Science, we identified 108 experimental studies. By evaluating multiple mechanisms, such as improving lipid metabolism and insulin resistance, alleviating oxidative stress damage, inhibiting liver inflammation, suppressing liver fibrosis, reducing endoplasmic reticulum stress, regulating hepatocyte autophagy, inhibiting hepatocyte apoptosis, improving mitochondrial dysfunction, and regulating the intestinal flora, we constructed a cross-scale regulatory network for the treatment of MAFLD by the active components of TCM. Subsequently, the dynamic target groups were screened, and a new paradigm of "mechanism-oriented and spatiotemporal-optimized" design for TCM compound prescriptions was proposed, providing a theoretical framework for the development of precise therapies that can improve liver lipid metabolism, block inflammation and fibrosis, and restore intestinal homeostasis.

Keywords: metabolic dysfunction-associated fatty liver disease, traditional Chinese medicine, active ingredient, lipid metabolism disorder, action mechanism

Introduction

With the growing prevalence of obesity and metabolic syndrome, metabolic dysfunction-associated fatty liver disease (MAFLD) has become the main cause of chronic liver disease worldwide. MAFLD affects 30% of adults globally, and its incidence is greater than 40% among individuals with diabetes and severe obesity. The prevalence is the highest in Asia-Pacific (32–35%), followed by the Middle East and Western nations. Over 20% of the cases of MAFLD show progression to advanced fibrosis within a decade, and these cases show a 5-fold higher risk of hepatocellular carcinoma (HCC).[1] Moreover, MAFLD imposes a substantial economic burden, with annual direct medical costs exceeding $100 billion globally, which are primarily driven by cirrhosis management and HCC treatments. This factor highlights the increasing demand for cost-effective treatment of MAFLD.

Received: 26 December 2024
Accepted: 31 March 2025
Published: 9 April 2025

MAFLD manifests as a spectrum of overlapping pathological states, including steatosis, inflammatory nonalcoholic steatohepatitis (NASH), fibrosis, and HCC, that progress through heterogeneous trajectories. Instead of showing a linear sequence, these states often coexist and interact through the crosstalk among metabolic dysfunction, oxidative stress, and chronic inflammation. Notably, fibrosis can develop independently of NASH in subsets of patients with specific genetic/metabolic risk profiles. Importantly, persistent inflammatory injury and advanced fibrosis (F3-F4) significantly elevate the risk of HCC, with epigenetic reprogramming and oncogenic signaling driving malignant transformation in a subset of MAFLD cohorts. This continuum underscores the need for personalized therapeutic strategies targeting multifactorial pathways, particularly interventions capable of interrupting the steatosis-inflammation-fibrosis-carcinogenesis axis.[2] The progression of MAFLD and its nonlinear characteristics can be represented by the flowchart shown in Figure 1.

The pathogenesis of MAFLD is influenced by many genetic and environmental factors, and is not fully understood at present. The conceptualization of MAFLD pathogenesis has been profoundly shaped by two landmark theories. The first of these theories, the "two-hit" hypothesis, proposed a sequential mechanism wherein the first hit (hepatic lipid accumulation driven by insulin resistance [IR] and de novo lipogenesis) primes the liver for the second hit (oxidative stress and inflammatory cascades triggering NASH and fibrosis). This framework revolutionized the field in the late 1990s by shifting the paradigm from passive lipid storage to dynamic cellular injury processes, providing the first mechanistic roadmap for therapeutic development.[3] Nevertheless, while the two-hit hypothesis yielded groundbreaking contributions, some critical limitations of this hypothesis gradually became evident. Clinical observations challenged its assumption of linear progression, since up to 28% of patients show advanced fibrosis without prior NASH, particularly those harboring PNPLA3 rs738409 polymorphisms. Subsequent studies demonstrated that lipid overload, mitochondrial dysfunction, and gut-derived endotoxins such as lipopolysaccharide (LPS) often coexist rather than follow a strict temporal sequence. Moreover, emerging evidence highlighted the role of extrahepatic crosstalk, wherein adipose tissue dysfunction and skeletal muscle IR independently exacerbate hepatic injury, mechanisms irreconcilable with the original two-step model.

These insights led to the "multiple parallel hit" theory, which emphasizes synchronized insults from metabolic dysregulation, epigenetic modifications, and microbiota-derived signals.[4] This paradigm shift directly informs our study's focus on traditional Chinese medicine (TCM) components with multiple targets, such as quercetin modulating the adenosine monophosphate (AMP)-activated protein kinase (AMPK)/sirtuin 1 (SIRT1)/farnesoid X receptor (FXR) pathways and berberine regulating proprotein convertase subtilisin/kexin type 9 (PCSK9)/nuclear factor (NF)-κB/liver X receptor (LXR) networks. The pleiotropic mechanisms underlying these effects inherently align with the need for combinatorial pathway modulation in MAFLD management.

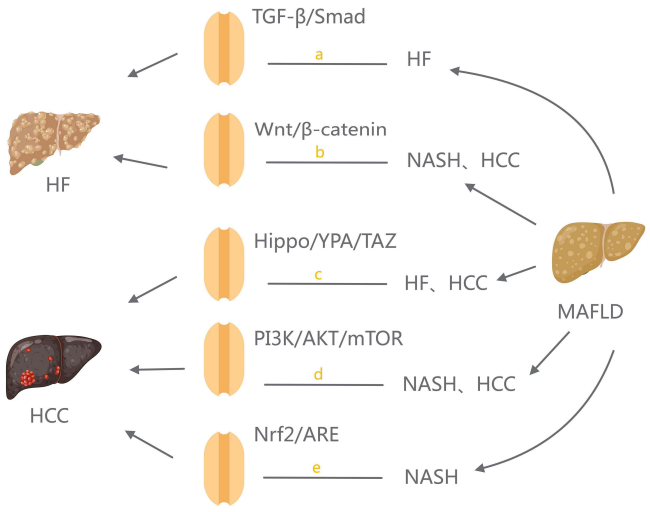

Figure 1 The progression of MAFLD and its non-linear characteristics.Upon activation, TGF-β collaborates with Wnt/β - catenin through Smad3 to promote fibrosis. The inactivation of the Hippo pathway leads to the nuclear translocation of YAP/TAZ, which then activates the PI3K/AKT/mTOR pathway, accelerating tumor progression. (a) TGF-β/Smad, Action stages: Hepatic Fibrosis (HF). (b) Wnt/β-catenin, Action stages: Non - alcoholic Steatohepatitis (NASH), Hepatocellular Carcinoma (HCC). (c) Hippo/YAP/TAZ, Action stages: HF, HCC. (d) PI3K/AKT/mTOR, Action stages: NASH, HCC. (e) Nrf2/ARE, Action stages: MAFLD, NASH.

MAFLD was originally known as nonalcoholic fatty liver disease. In 2020, a panel of experts from 22 countries proposed a new definition that is internationally independent of other liver diseases, renaming this condition as MAFLD to more accurately reflect its association with metabolic disorders.[5] The newly proposed MAFLD framework also aligns with the holistic approach of TCM treatment. For example, berberine simultaneously improves insulin sensitivity, reduces hepatic fat synthesis, and regulates gut microbiota. Current first-line therapies, such as vitamin E and pioglitazone, have limited efficacy and pose risks of cardiovascular complications and osteoporosis with long-term use. Although dietary modification and exercise remain the cornerstones of MAFLD treatment and management, 80% of patients are unable to adhere to lifestyle interventions for more than six months. In contrast, the multi-target mechanisms and formulation flexibility of TCM can synergistically regulate pathways involved in lipid oxidation, inflammation, and fibrosis, reducing or even eliminating the occurrence of these adverse reactions and making TCM a viable option for patients who have difficulty adhering to dietary control. Considering the nonlinear progression, concurrent triggers, and organ interactions in the pathogenesis of MAFLD, the multi-target strategy of TCM can address the complexity of MAFLD more effectively than single-pathway drugs, highlighting the increasing importance of the TCM paradigm in metabolic disease research.

A growing number of experimental studies have confirmed the advantages of the active ingredients of TCM formulations in preventing and improving MAFLD.[6] In the present study, we used keywords such as "MAFLD", "traditional Chinese medicine", and "active ingredient" to search for relevant English-language literature published on PubMed and Web of Science in the past decade. The inclusion criteria covered experimental studies and studies exploring therapeutic mechanisms, while case reports and irrelevant studies were excluded. This study investigated MAFLD by reviewing data obtained through phytochemical and pharmacological experimental designs and systematically constructed a cross-scale regulatory network of TCM active ingredients for treating MAFLD. Subsequently, a new paradigm of TCM compound design, "mechanism-oriented, spatiotemporal optimization", was proposed by screening dynamic target populations. This model provides a theoretical framework for the development of precision treatment modalities that can simultaneously improve hepatic lipid metabolism, block inflammation and fibrosis, and restore gut homeostasis.

Common Mechanisms of Action of TCM Active Ingredients in the Treatment of MAFLD

Numerous experimental studies have evaluated the mechanisms of action of TCM active ingredients in the treatment of MAFLD. Relatively stable animal models of MAFLD have been established by feeding animals high-fat diets (HFDs) or methionine-choline deficient (MCD) diets. The active components of TCM can antagonize the occurrence and development of MAFLD at several interrelated levels. Their mechanisms of action are mainly related to improving lipid metabolism and IR, alleviating oxidative stress damage, inhibiting liver inflammation, inhibiting liver fibrosis, alleviating endoplasmic reticulum stress (ERS), regulating hepatocyte autophagy, inhibiting hepatocyte apoptosis, improving mitochondrial dysfunction, and regulating intestinal flora. The basis for classification of TCM active ingredients used for the treatment of MAFLD is presented in Figure 2. The mechanisms of action of these ingredients are summarized in the following paragraphs.

Improving Lipid Metabolism Disorders and IR

The liver is the most active organ in lipid metabolism in the body, and it participates in the digestion, absorption, transportation, catabolism and anabolism of fat. Disruptions in lipid metabolism may lead to increased synthesis and decreased breakdown of fat in the liver, and the resultant lipid overload in liver cells may eventually lead to MAFLD, which is closely related to IR and genetic susceptibility. Abnormal lipid metabolism, especially the metabolic imbalance of free fatty acids (FFA), low-density lipoprotein (LDL), triacylglycerol (TG), and total cholesterol (TC), can directly or indirectly lead to MAFLD.[7] Therefore, targeting the overload of serum FFA, LDL, TG, TC and aspartate aminotransferase (AST) levels and increasing the production of high-density lipoprotein (HDL-C) can effectively improve liver lipid metabolism and reduce liver metabolic stress, thereby playing a positive therapeutic effect on MAFLD. AMPK is a key regulator of energy metabolism, and its phosphorylation can inhibit the biosynthesis of cholesterol, fatty acids, and

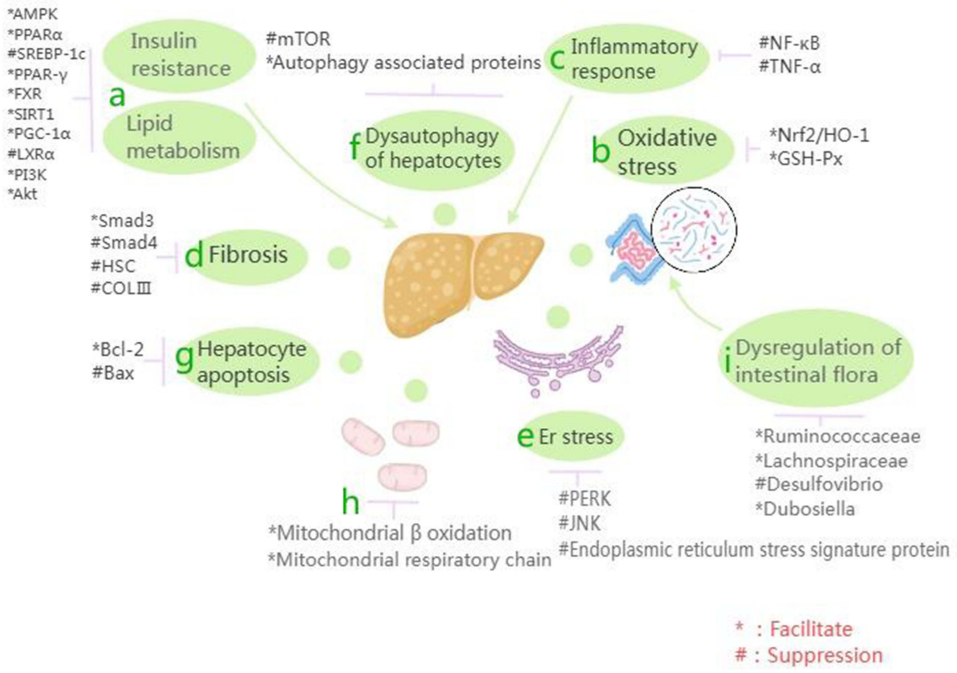

Figure 2 Classification basis of MAFLD of active ingredients of traditional Chinese medicine *, To increase, promote, or increase;#, To reduce, inhibit, or reduce. (a) Improve lipid metabolism disorders and insulin resistance: AMPK, PPARα, SREBP-1c, PPAR-γ, FXR, SIRT1, PGC-1α, LXRα, PI3K, AKt. (b) Relieve oxidative stress: Nrf2/HO-1, GSH-Px. (c) Inhibit liver inflammation: NF-κB, TNF-α. (d) Inhibit liver fibrosis: Smad3, Smad4, HSC, COLIII. (e) Relieve endoplasmic reticulum stress: PERK, JNK, Endoplasmic reticulum stress signature protein. (f) Regulate autophagy of hepatocytes: mTOR, Autophagy associated proteins. (g) Inhibition of hepatocyte apoptosis: Bcl-2, Bax. (h) Improve mitochondrial dysfunction: Mitochondrial β oxidation, Mitochondrial respiratory chain. (i) Improve intestinal flora imbalance: Ruminococcaceae, Lachnospiraceae, Desulfovibrio, Dubosiella.

triglycerides, thereby reducing lipid deposition in the liver.[8] Various active ingredients of TCM formulations exert therapeutic effects by specifically regulating the AMPK pathway, including puerarin,[9] alisol a,[10,11] *Lonicera caerulea* extract,[12] crocin,[13] dihydromyricetin (DHM),[14] betaine,[15] *Lycium barbarum* polysaccharides (LBP),[16] ursolic acid,[17] Radix Hedysari polysaccharide,[18] kaempferol (KAP),[19] *Leonurus* ethanol extract,[20] gardenin,[21] *Magnolia officinalis* extract,[22] ginsenoside Rb2,[23] atractylenolide III,[24] green tea extract,[25] gastrodin,[26] coix seed extract,[27] licorice extract,[28] and *Scutellaria baicalensis*.[29] Crucially, the components of TCM harness the spatiotemporal regulatory plasticity of AMPK to achieve optimized effects in different tissues. For example, ginsenoside Rb2 enhances the phosphorylation of the AMPKα1-Ser485 site, promoting the translocation of glucose transporter 4 (GLUT4) without triggering inflammatory NF-κB feedback regulation like pan-AMPK activators do. Resveratrol synchronizes the circadian oscillations of AMPK with the rhythms of butyrate produced by gut microbiota, enhancing lipid oxidation through co-activation with peroxisome proliferator-activated receptor alpha (PPARα). This multi-tiered regulatory approach, which takes advantage of the isoform specificity of AMPK, the diversity of phosphorylation sites, and circadian dynamics, demonstrates how the inherent polypharmacology of TCM can address the complexity of MAFLD, which is beyond the capabilities of single-target drugs.[30] Chlorogenic acid (CGA) is a natural polyphenol widely found in plants. It can regulate autophagy by specifically binding to AlkB homolog 5 (ALKBH5) to inhibit its m6A methylase activity and improve liver lipid deposition in HFD-fed mice by activating AMPK.[31] Panpan Liu et al used network pharmacology methods and observed that KAP can prevent the occurrence and development of MAFLD through multiple targets such as inhibiting inflammation, improving IR, and reducing oxidative stress. Through cell and animal experiments, they also confirmed that KAP can inhibit the inflammatory response both in vitro and in vivo by suppressing the nuclear transcriptional activity of NF-κB, thereby preventing the occurrence of MAFLD.[32] Baicalein has been confirmed to reduce hepatic fat accumulation by activating AMP-AMPK and inhibiting the cleavage of sterol regulatory element-binding protein 1 (SREBP1). This, in turn, suppresses the transcriptional activity of SREBP1 and the synthesis of hepatic fat in oleic acid-induced HepG2 cells and HFD-induced non-insulin-resistant mice. Moreover, baicalein can decrease TC and LDL-C

levels while increasing HDL-C levels, thereby ameliorating the progression of MAFLD.[33] Myricetin extracted from sea buckthorn can slow down the progression of MAFLD in HFD rats. Myricetin shows these effects by reducing the levels of TC, TG, alanine transaminase (ALT), and aspartate aminotransferase (AST) through multiple means, such as activating AMP-AMPK, improving the key gut microbiota system, and decreasing the levels of tumor necrosis factor (TNF)-α and interleukin (IL)-6 in the plasma, liver, and colon.[34] In addition, regulation of the LXR and sterol regulatory element-binding protein 1c (SREBP1c) pathways by the components of TCM is equally crucial. The LXR is involved in regulating cholesterol balance, inhibiting inflammation and improving IR. Inhibition of LXR transcriptional activity can improve liver steatosis, reduce inflammation, and prevent the development of liver fibrosis.[35] Ursolic acid,[17] tanshinone IIA,[36] and diosgenin[37,38] can improve lipid accumulation in liver cells by antagonizing LXR alpha (LXRa). *Leonurus* ethanol extract can improve liver β-oxidation by upregulating the AMPK lipid metabolism signaling pathway and PPARα expression.[20] Activation of AMPK negatively regulates SREBP-1c, thereby ameliorating lipid metabolism disorders. SREBP-1c, one of the components of sterol regulatory element-binding protein (SREBPs), is a key regulator of lipid and cholesterol metabolism in the liver, and is one of the important targets of the effective active ingredients of TCM in the treatment of MAFLD, such as *Schisandra* polysaccharides,[39] alisol a,[11] *Sargassum fusiforme* polysaccharide (SFPS),[40] *Ophiopogon* polysaccharide (MDG),[41,42] oroxin A,[43] and oroxin B.[44] Acerola polysaccharides (ACPs) are a potent active ingredient of conifers, and the results of the study showed that ACPs inhibited liver SREBP1-c levels in mice, significantly improving the accumulation of liver lipid in mice fed HFD.[45] IR refers to a state characterized by reduced efficiency of insulin in promoting glucose uptake and utilization, resulting in a compensatory state of hyperinsulinemia. IR plays a central role in the mechanism and development of MAFLD by triggering disorders in glucose and lipid metabolism in the liver, as well as chronic inflammation and oxidative stress.[46] TCM ingredients such as *Angelica* polysaccharide,[47] emodin,[48] and silibinin[49] exhibit multi-target characteristics to improve IR. Berberine (BBR) is the active ingredient of *Coptis chinensis*. BBR preferentially activates the AMPK α2 isoform by phosphorylating the Thr172 site, suppressing SREBP-1c-mediated lipogenesis without affecting muscle glucose uptake.[50] BBR may also inhibit liver fatty acid consumption by reducing the expression of SCD1, FABP1, CD36 and CPT1A, and activating AMPK phosphorylation to improve IR, thereby inhibiting lipid metabolism.[51] The relevant active ingredients of TCM formulations and their mechanisms of action are shown in Table 1.

Table 1 Summary of Experimental Studies on the Effects of Active Components of Traditional Chinese Medicine on the Treatment of MAFLD by Improving Lipid Metabolism Disorder and Insulin Resistance

Active Ingredient	Source	Pharmacological Model	Pharmacological Mechanism	Reference
Puerarin	*Pueraria lobata*	HepG2 cells treated with oleic acid	Activates AMPK/PPARα → Inhibits SREBP-1c → ↓TG/TC	[9]
Alisol A	Alismatis Rhizoma	Mice fed an HFD	↑ABCA1/ABCG1 → ↓LDL-C, ↑HDL-C; Activates AMPK → Inhibits SREBP-1c/ACC	[10,11]
Lonicera caerulea extract	*Lonicera caerulea*	Mice fed an HFD	Activates AMPK/PPARα → ↑CPT-1 → ↑Fatty acid β-oxidation	[12]
Crocin	Saffron *Crocus*	DB/DB mice fed an HFD	Activates AMPK → ↑Fatty acid β-oxidation	[13]
Dihydromyricetin	Hairy grape	Rats fed an HFD; HepG2 cells treated with palmitic acid	Activates AMPK/PPARα/PGC-1α → ↓IR	[14]
Betaine	Beet molasses	Mice fed an HFD	Activates AMPK → Inhibits ACC → ↓ER stress	[15]

(*Continued*)

Table 1 (Continued).

Active Ingredient	Source	Pharmacological Model	Pharmacological Mechanism	Reference
Lycium barbarum polysaccharide	Wolfberry	Rats fed an HFD	Activates AMPK/PPARα/PGC-1α → ↑Fatty acid β-oxidation	[16]
Ursolic acid	Ursolic	Mice fed an HFD	Activates AMPK → Inhibits SRC-1/Liver X receptor	17]
Radix Hedysari polysaccharide	Radix Hedysari	Rats fed an HFD	Activates AMPK/PPARα → Inhibits SREBP-1c → ↓LDL-C/AST/ALT	[18]
Kaempferol	Sand Ginger	DB/DB mice	Activates AMPK/SIRT1/PGC-1α → Inhibits SREBP1/ACC	[19]
Kaempferol	Tea, Broccoli, Propolis, Grapefruit	HepG2 cells treated with OA;Male SPF SD rats fed an HFD	↓NF-κB (in the nucleus); ↑NF-κB (in the cytoplasm); Inhibits NF-κB↓→TNFα/IL 6/→↓Fibrosis/Inflammation;↓ALT/AST/TC/TG	[32]
Leonurus ethanol extract	*Leonurus*	Mice fed an HFD	Activates AMPK/PPARα	[20]
Gardenin	Gardenia	Mice fed a Tetrabut	Activates AMPK/Nrf2 → Inhibits mTOR	[21]
Magnolia officinalis extract	*Magnolia officinalis*	Mice fed an HFD	Activates AMPK	[22]
Ginsenoside Rb2	Ginseng	DB/DB mice	Activates AMPK/SIRT1	[23]
Atractylenolide III	*Atractylodes* rhizome	Mice fed an HFD	Activates AMPK/SIRT1	[24]
Green tea extract	Green tea	Mice fed an HFD	Activates AMPK/SIRT1 → ↑Adiponectin receptor 2 → ↓FFA	[25]
Gastrodin	*Gastrodia elata*	Mice fed an HFD	Activates AMPK	[26]
Coix seed extract	Coix seed	Rats fed an HFD	Activates AMPK → ↓SePP1/apoER2 → ↓TC/TG	[27]
Licorice extract	Licorice	Mice fed an HFD	Activates AMPK/SIRT1 → ↑Fatty acid β-oxidation	[28]
Scutellaria baicalensis	Skullcap	MAFLD rats treated with OA	Activates AMPK → Inhibits SREBP-1c	[29]
CGA	*Artemisia capillaris*	Mice fed an HFD	Activates AMPK/ULK-1 → Inhibits AXL/ERK/LKB1	[31]
Tanshinone IIA	*Salvia miltiorrhiza*	HepG2 cells and Huh7 cells treated with FFA	Inhibits liver X receptor α → ↓ACC1/FAS	[36]
Diosgenin	Dioscorea, legumes, ginger and other plants	Mice fed an HFD	Activates AMPK/SIRT-1 → ↑CPT-1 → Inhibits SREBP-1c/LXRa	[37,38]
Schisandra polysaccharides	*Schisandra chinensis*	Mice fed an HFD	Inhibits SREBP-1c → ↓ACC/FAS	[39]
Sargassum fusiforme polysaccharide	*Sargassum fusiforme*	*Drosophila* larvae treated with high sugar	Activates PPARα → Inhibits SREBP → ↓TG/FAS	[40]
Ophiopogon polysaccharide	Liriope	Mice fed an HFD	Activates AMPK/PPARα → Inhibits SREBP-1c → ↓TG/TC	[41,42]

(*Continued*)

Table 1 (Continued).

Active Ingredient	Source	Pharmacological Model	Pharmacological Mechanism	Reference
Acerola polysaccharides	Coniferous tree	Mice fed an HFD	Inhibits SREBP-1c → ↓TG/TC; ↑PGC-1α → ↓UCP2 →↑Mitochondrial β-oxidation	[45]
Angelica polysaccharide	*Angelica*	Mice fed an HFD	Activates PI3K/Akt → ↓IR	[47]
Emodin	Rhubarb	Mice fed an HFD	Activates FXR → ↓TG/IR	[48]
Silbinin	*Silybum*	Rats fed an HFD	Activates IRS/PI3K/Akt → ↓IR	[49]
Berberine	*Coptis chinensis*	Mice fed an HFD	Activates AMPK → ↓FABP1/SCD1/CD36 → ↑CPT1A →↓IR	[50]
Ginkgo biloba polysaccharide	*Ginkgo biloba* leaf	Rats fed an HFD	↓IR	[52]
Ginsenoside Rb1	Ginseng	Mice fed an HFD	Activates PPAR-γ → ↓Hepatocyte apoptosis	[53]
MP-A	Mussel	Rats fed an HFD	↓TG/TC	[54]
Curcumin	*Curcuma*	Rats fed an HFD; LSEC cells and L02 cells treated with FFA	Inhibits NF-κB/PI3K/Akt/HIF-1α	[55]
Betulinic acid	Silver birch	Mice fed an HFD	Inhibits YY1 → ↓FAS	[56]
Acanthoic acid	Acanthoderm	Mice fed an HFD	Activates AMPK/SIRT1	[57]
Triptolide	Thunder God vine	DB /DB Mice fed with HFD	Activates AMPK → ↑Fatty acid β-oxidation → ↓Fibrosis	[58]
Enteromorpha polysaccharides	*Enteromorpha*	Rat fed with HFD	↑CBS/CSE/H_2S → ↓TG/TC	[59]
Alisma orientalis extract	*Alisma orientalis*	Rat fed with HFD	Activates AMPK/PPARα → ↑Fatty acid β-oxidation → ↓Hepatocyte apoptosis/IR	[60]
Quercetin	Raspberries, *Ginkgo biloba*	DB/DB Mice; HepG2 cells treated with FFA	Inhibits mTOR/YY1 → ↑CYP7A1	[61]
Catalpol	*Rehmannia* root	Mice fed an HFD	Activates AMPK → ↑Fatty acid β-oxidation	[62]
Baicalein	*Scutellaria baicalensis*	Mice fed an HFD; HepG2 cells treated with OA	Activates AMPK →Inhibits SREBP1→ ↓IR→↓TC/LDL-C/ ↑HDL-C	[33]
Myricetin	Sea buckthorn	Rats fed an HFD	[Activates AMPK →InhibitsACC/HMGCR;InhibitsLPS/TLR4/ NF-κB→↓TNF-α→↓IL-6;↑Dermabacteriaceae / Coriobacteriaceae / Allobaculum/ Brachybacterium]→↓TC/ TG/ALT/AST	[34]
Oroxin A	*Oroxylum indicum*	Rats fed an HFD; HepG2 cells treated with OA	Inhibits SREBP1→Inhibits ACC/FASN→↓TG;Inhibits SREBP2→Inhibits HMGCR→↓TC Unites LDLR→Activates AMPK	[43]
Oroxin B	*Oroxylum indicum*	Rats fed an HFD	↓Lipin/LPS;Inhibits TLR4-IκB-NF-κB-IL-6/TNF-α;↑ZO-1/ZO-2;↓*Tomitella/Bilophila/Acetanaerobacterium / Faecalibaculum*	[44]

Note: ↑indicates upward, promotion, or increase; ↓indicates downward adjustment, suppression, or reduction.

https://doi.org/10.2147/DDDT.S514498

Relieving Oxidative Stress

The lipotoxic microenvironment caused by lipid metabolism disorders further exacerbates excessive production of reactive oxygen species (ROS). Oxidative stress refers to a state wherein excessive production of free radicals due to stimulation by mitochondrial ROS as a result of hyperglycemia, inflammatory signals, or exogenous toxins overwhelms the body's ability to scavenge these free radicals, causing disorders of the body's reduction-oxidation system. Oxidative stress is one of the important reasons for the occurrence and development of MAFLD, so alleviating oxidative stress-induced damage is a key objective of the treatment of MAFLD. Many active ingredients of TCM formulations have been shown to alleviate oxidative stress, including *Codonopsis lanceolata* polysaccharide (CLPS),[63] salvianolic acid B,[64] 2,3,4′,5-tetrahydroxystilbene-2-0-β-D-glycoside,[65] and OISE.[66] At the molecular regulation level, activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase (HO-1) signaling pathway is a classic antioxidant strategy. For example, aucubin promotes the expression of antioxidant genes by enhancing the nuclear translocation of Nrf2.[67] *Sagittaria sagittifolia* polysaccharide specifically upregulates the activity of HO-1, synergistically improving lipid metabolism disorders.[68] Notably, *Ganoderma lucidum* polysaccharide alleviates hepatic steatosis through this pathway and significantly increases the levels of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), forming a dual-defense mechanism.[69] Jingda Li et al observed that hesperetin improves hepatic oxidative stress through the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)-Nrf2 pathway, and this antioxidant effect further inhibits NF-κB-mediated inflammation during the progression of MAFLD.[70] The components of TCM formulations have also shown the ability to intervene precisely in the pathological cascade reactions mediated by ROS. Polydatin is a combination of resveratrol and glucose. In comparison with resveratrol, polydatin has stronger antioxidant effect and stability. Polydatin has been shown to inhibit lipid peroxidation through antioxidants. It reduces Keap1 expression and enhances the Nrf2 antioxidant pathway, and it slows down the ROS-driven thioredoxin-interacting protein (TXNIP) activation of the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome process, improves lipid metabolism, and reduces BRL-3A cell inflammation and lipid deposition.[71] Moreover, recent studies have redefined the role of ROS as dynamic signaling mediators in the pathogenesis of MAFLD. Although excessive ROS can lead to hepatocyte damage, ROS at physiological levels in the liver and adipose tissue can activate adaptive responses. Mitochondria-derived ROS can enhance the antioxidant defense mechanism mediated by Nrf2, and work in concert with AMP-AMPK to optimize lipid metabolism.[72] Crucially, tissue-specific regulation is involved in these mechanisms. Hepatocytes preferentially utilize SOD2 for ROS detoxification, while adipocytes rely on the interaction between catalase and AMP-AMPK. This duality highlights the therapeutic opportunities presented by multi-target components of TCM formulations, such as resveratrol. Their multi-target advantages hold the promise of selectively scavenging pathological ROS while preserving the ROS levels required for beneficial signaling—a balance that conventional antioxidants cannot achieve. The relevant active ingredients of TCM and their mechanisms of action are shown in Table 2.

Table 2 Summary of Experimental Studies on the Effects of Active Components of Traditional Chinese Medicine on MAFLD by Relieving Oxidative Stress

Active Ingredient	Source	Pharmacological Model	Pharmacological Mechanism	Reference
Codonopsis lanceolata polysaccharide	Fir	Mice fed a high-fat, high-sucrose diet	Activates Nrf2 → ↑HO-1/SOD → ↓ROS → ↓IR	[63]
Salvianolic acid B	*Salvia miltiorrhiza*	Rats fed an HFD	Inhibits CYP2E1 → ↓ROS → ↓Hepatocyte apoptosis; Activates PPARγ → ↓TG/TC	[64]

(*Continued*)

Table 2 (Continued).

Active Ingredient	Source	Pharmacological Model	Pharmacological Mechanism	Reference
2,3,4′,5-tetrahydroxystilbene-2-0-β-d glycoside	*Polygonum multiflorum*	Mice fed an HFD	Inhibits SREBP-1c → Inhibits ACC/FASN; Activates PPARα → ↑CPT-1 → ↓Lipid accumulation; Inhibits CYP2E1 → ↓Oxidative stress → ↓Fibrosis	[65]
Aucubin	Honeysuckle	Male C57/BL6 Mice	Activates AMPK → Activates PPARα → ↑Fatty acid β-oxidation; Activates Nrf2/HO-1 → ↓Oxidative stress → ↓TC/TG	[67]
Sagittaria sagittifolia polysaccharide	*Sagittaria sagittifolia*	Mice fed an HFD	Activates Nrf2 → ↑GSH/GST → ↓Oxidative stress	[68]
Ganoderma lucidum polysaccharide	*Ganoderma lucidum*	DB/DB mice fed an HFD	Activates Nrf2/HO-1 → ↑SOD/CAT → ↓ROS; Inhibits NF-κB → ↓TNF-α	[69]
Polydatin	Knotweed root, *Polygonum multiflorum* root	SD rats fed with levulose	Inhibits Keap1 → ↑Nrf2 nuclear translocation → ↑ARE genes → ↓ROS/Oxidative stress	[71]
Chicory polysaccharide	Chicory	Rats fed an HFD	Activates AMPK → Activates PPARα → Inhibits SREBP-1c → ↓TC/TG; ↓Oxidative stress	[73]
Hesperetin	Oranges, grapefruit, lemons	HepG2 cells treated with OA; Rats fed an HFD	Activates PI3K/AKT-Nrf2→↑SOD/GPx/GR/GCLC/HO-1; Inhibits NF-κB→↓TNF-α / IL-6	[70]
OISE	*O. indicum* seed	HepG2 cells treated with OA; Rats fed an HFD	Inhibits NF-κB→↑IκB→↓Inflammation/Oxidative stress	[66]

Note: ↑indicates upward, promotion, or increase; ↓ indicates downward adjustment, suppression, or reduction.

Inhibiting Liver Inflammation

Excessive accumulation of ROS directly damages liver cells and also triggers a persistent inflammatory response by activating inflammatory signaling pathways. Liver inflammation plays a crucial role in the progression of MAFLD. This inflammatory state drives exacerbation of the disease through a dual mechanism: on one hand, pro-inflammatory factors such as TNF-α and IL-6 exacerbate intrahepatic lipid deposition; on the other hand, these factors promote collagen secretion by activating hepatic stellate cells, leading to the transition of simple fatty liver through the stages of steatohepatitis and fibrosis.[74] At the level of inflammation regulation, the active ingredients of TCM formulations block this vicious cycle by targeting key signaling nodes. For example, LBP block the nuclear translocation of NF-κB by inhibiting the formation of the TLR4-MyD88 complex.[75,76] Tetramethylpyrazine (TMP), on the other hand, simultaneously improves mitochondrial dysfunction and apoptosis by downregulating the phosphorylated NF-κB (p-NF-κB)/ROS signaling axis.[77] Notably, andrographolide directly inhibits the phosphorylation cascade reaction of NF-κB by specifically binding to the kinase domain of inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ), and its inhibitory effect exhibits a dose-dependent characteristic.[78] More recent studies have revealed the central role of the metabolism-immunity interaction in the inflammation of MAFLD. Metabolites such as succinate and palmitic acid can directly activate the NLRP3 inflammasome in macrophages. However, berberine breaks this association through a dual effect: it inhibits the signal transduction of succinate and reprograms the metabolic pattern of macrophages to be dominated by oxidative phosphorylation via the AMPK-peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC1α) pathway. This metabolic remodeling reduces the release of pro-inflammatory factors and improves the intrahepatic lipid microenvironment by enhancing fatty acid β-oxidation.[79] In addition, the multi-target characteristics of TCM components, such as LBP, paeonin,[80] *Poria cocos* extract,[81] *Perilla* oil supplementation (ALA),[82] *Tremella*

https://doi.org/10.2147/DDDT.S514498

polysaccharide,[83] nucifoline,[84] *Cassia* semen ethanol extract,[85] and gypenosides,[86] demonstrate unique advantages in the complex inflammatory network. This network-based regulation mode breaks through the limitations of single-target drugs and provides new ideas for improving the long-term prognosis of patients with MAFLD. The relevant active ingredients of TCM and their mechanisms of action are shown in Table 3.

Inhibiting Liver Fibrosis

A sustained inflammatory response promotes the activation of stellate cells, which is a key triggering factor for liver fibrosis. Liver fibrosis is a pathological process caused by various chronic liver injuries, and it is an important part of fatty liver disease. In this process, excessive deposition of collagen, mucin, and other extracellular matrix components in the liver and reduced degradation of these components result in abnormal liver structure and function. Liver fibrosis is considered to be a dynamic and reversible process. If the underlying cause is removed or controlled in time, liver fibrosis can be reversed to varying degrees. This finding provides a new direction for the treatment of MAFLD to slow or even reverse the progression of the disease by suppressing liver inflammation and improving liver fibrosis. The active ingredients of TCM formulations have shown obvious advantages in the treatment of liver fibrosis, including oxymatrine,[88] andrographolide,[78] and gypenoside LXXV.[89] Precise interventions targeting the key nodes of fibrosis has achieved breakthroughs in recent studies. For example, the total glucosides of peony (TGP) can specifically bind to the promoter region of NLRP3 and inhibit its transcriptional activity by inducing the expression of the transcription factor FLI1. This epigenetic regulatory mechanism can alleviate hepatocyte apoptosis and block the progression of fibrosis by remodeling the immune microenvironment.[90] In addition, glycyrrhizic acid (GA) shows unique

Table 3 Summary of Experimental Studies on the Effects of Active Components of Traditional Chinese Medicine on MAFLD by Inhibiting Liver Inflammation

Active Ingredient	Source	Pharmacological Model	Pharmacological Mechanism	Reference
Lycium barbarum polysaccharides	*Lycium barbarum*	Mice fed an HFD	Inhibits NLRP3/NF-κB → ↓Inflammation/Oxidative stress	[75]
Lycium barbarum polysaccharide	*Lycium barbarum*	Rats fed an HFD	↓FFA/IR; ↓Oxidative stress/Inflammation	[76]
Paeonin	Peony	Mice fed an HFD	Activates PPARα → ↓Inflammation/IR	[80]
Poria cocos extract	*Poria cocos*	Mice fed an HFD	Activates PPARα/FXR; Inhibits SREBP-1c/CYP7A1 → ↓TC/TG/Inflammation	[81]
ALA	Perilla	Rats fed an HFD	↓Fibrosis/Inflammation	[82]
Tremella polysaccharide	*Tremella*	Mice fed an HFD	Inhibits TLR4 → ↓IL-1β/TNF-α/IL-6; Activates HNF4α → ↓Inflammation/Oxidative stress	[83]
Andrographolide	*Andrographis paniculata*	Mice fed CDAA	Inhibits NF-κB → ↓Oxidative stress/Inflammation	[78]
Nucifoline	Lotus	Rats fed an HFD	↓Oxidative stress/Inflammation	[84]
Cassia semen ethanol extract	*Cassia* semen	Rats fed an HFD	Inhibits TNF-α/IL-6/IL-8 → ↓Inflammation; ↓AST/ALT/TG/TC	[85]
Gypenosides	*Gynostemma pentaphyllum*	Rats fed an HFD	Inhibits SREBP-1c; Activates CPT-1 → ↓TG/FFA/Oxidative stress/Inflammation	[86]
TMP	*Ligusticum wallichii*	Mice fed an HFD	Inhibits p-NF-κB → ↓NF-κB activity/ROS → ↓Inflammation	[77]
Salidroside	*Rhodiola rosea*	Mice fed an HFD	Activates AMPK → ↓IR/Oxidative stress; Inhibits NLRP3 → ↓Inflammation	[87]

Note: ↑ indicates upward, promotion, or increase; ↓ indicates downward adjustment, suppression, or reduction.

multi-target effects: while inhibiting collagen deposition, it reduces de novo lipogenesis by downregulating the SREBP-1c/FAS pathway and activates PPARα to enhance fatty acid oxidation, achieving a triple synergy of anti-fibrosis, lipid metabolism-regulating, and anti-inflammatory effects.[91] Notably, the spatiotemporal dynamic regulatory characteristics of TCM components represent an advantage in the management of complex pathological networks. For example, eugenol selectively inhibits the cyclooxygenase (COX)-2/prostaglandin E2 (PGE2) inflammatory pathway through a phase-separated mechanism,[92] while schisandrin B enhances the antioxidant reserve of hepatocytes through the Nrf2-GSH axis.[93] This hierarchical defense system can target the driving factors of fibrosis and create microenvironmental conditions facilitating hepatocyte repair. The relevant active ingredients of TCM and their mechanisms of action are shown in Table 4.

Relieving ERS

In addition to disrupting the structure of the liver, abnormal deposition of the extracellular matrix during the process of fibrosis also exacerbates metabolic imbalance by interfering with the functions of lipid synthesis and protein folding in the endoplasmic reticulum (ER). The "multiple-hit" theory proposed in recent years emphasizes that ERS is the core mechanism for the progression of MAFLD to NASH. By activating unfolded protein response (UPR) signals (such as the inositol-requiring enzyme 1α [IRE1α]–X-box binding protein 1 [XBP1] pathway), ERS induces the expression of inflammatory factors and inhibits the secretion of apolipoproteins, thus forming a vicious cycle of lipotoxicity and inflammation.[95] At the level of ERS regulation, the active ingredients of TCM formulations restore ER homeostasis by targeting key nodes. Betulinic acid (BA) blocks the apoptosis signal-regulating kinase 1 (ASK1)- c-Jun N-terminal kinase (JNK) apoptotic signaling cascade by inhibiting the kinase activity of IRE1α.[96] Resveratrol, on the other hand, alleviates the translational inhibition caused by the excessive activation of the protein kinase R-like ER kinase (PERK) pathway by enhancing the SIRT1-dependent deacetylation of eIF2α.[97] Notably, catalpol can simultaneously down-regulate the expression levels of binding immunoglobulin protein (BiP) and IRE1α. Its dual inhibitory effect reduces the ERS markers in hepatocytes by more than 65% and significantly decreases the levels of serum TG/TC in HFD mice, demonstrating synergistic beneficial effects

Table 4 Summary of Experimental Studies on the Effects of Active Components of Chinese Medicine on MAFLD by Inhibiting Liver Fibrosis

Active Ingredient	Source	Pharmacological Model	Pharmacological Mechanism	Reference
Oxymatrine	*Sophora flavescens*	Rats fed an HFD	Activates PPARα; Inhibits SREBF1/SREBP1 → Inhibits ACC/FAS → ↓Fibrosis	[88]
Eugenol	Clove, cinnamon	Mice fed an HFD	Activates AMPK → Inhibits SREBP1/mTOR → ↓TG/Fibrosis	[92]
Andrographolide	*Andrographis paniculata*	Mice fed CDAA	Inhibits NF-κB → ↓Inflammation/Fibrosis	[78]
Gypenoside LXXV	*Gynostemma pentaphyllum*	Mice fed an HFD	Inhibits α-SMA/TNF-α/GRP78 → ↓Fibrosis	[89]
Schisandrin B	*Schisandra chinensis*	Mice fed an HFD	Activates Nrf2; Inhibits SREBP-1 → Inhibits FAS → ↓Oxidative stress/Fibrosis	[93]
TGP	Radix paeoniae alba	Fibrotic mice treated with CCl_4	Activates FLI1; Inhibits NLRP3 → ↓COLIII/COLIV → ↓Fibrosis	[90]
GA	Licorice	Mice fed an HFD	Activates PPARα; Inhibits SREBP-1c → Inhibits ACC1/SCD1/FAS; Inhibits MCP-1/VCAM-1 → ↓Inflammation/HSC activation → ↓Fibrosis	[91]
Fuzheng huayu recipe	*Salvia miltiorrhiza*, Peach kernel, Pine pollen, Fermented cordyceps powder, *Schisandra chinensis*, Gynostaphylla	Mice fed an MCD diet	Inhibits IKK-β/NF-κB → ↓MCP-1/Inflammation; Inhibits Smad3/Smad4; Activates Smad7 → ↓Fibrosis; ↓Oxidative stress	[94]

Note: ↑ indicates upward, promotion, or increase; ↓ indicates downward adjustment, suppression, or reduction.

on ERS regulation and lipid metabolism. Catalpol is an active ingredient extracted from *Rehmannia* root. It shows many biological activities such as anti-inflammation and anti-apoptosis activities. Catalpol can significantly reduce the expression of key proteins involved ERS, such as BiP and IRE1α. By alleviating ERS, catalpol can reduce the expression of proteins associated with apoptosis, thereby inhibiting the apoptosis process of hepatocytes. In addition, catalpol can significantly reduce serum TG and TC levels in mice fed HFD, thereby improving the symptoms of MAFLD.[98] The relevant active ingredients of TCM and their mechanisms of action are shown in Table 5.

Regulating Autophagy of Hepatocytes

The alleviation of ERS creates the necessary microenvironmental conditions for the dynamic regulation of the autophagy system. MAFLD is characterized by hepatic lipid accumulation that exceeds the metabolic capacity of the liver, resulting in lipid overload within liver cells. In addition to affecting the normal functioning of the liver, this lipid overload also reduces fat autophagy, which, in turn, slows the self-degradation of lipids to create a vicious cycle. Therefore, regulation of hepatocyte autophagy is of great importance in the treatment of MAFLD. At the level of autophagy regulation, the active ingredients of TCM formulations restore the autophagic flux by targeting different links. Resveratrol promotes the formation of autophagosomes by activating the AMPK-Unc-51-like kinase 1 (ULK1) phosphorylation cascade.[99] Puerarin, on the other hand, increases the biosynthesis of lysosomes by enhancing the nuclear translocation of transcription factor EB (TFEB), which improves the autophagic degradation efficiency by 2.3-fold.[100] Notably, bergamot polyphenols (BPF) significantly accelerate the clearance of lipid droplets and damaged organelles by synergistically upregulating the levels of the LC3-II/Beclin1 complex and reducing the expression of p62. The effect of BPF in promoting the autophagic flux has been verified through liver ultrasound imaging and liver histological examinations.[101] Considering the complexity of the autophagy regulation network, the components of TCM formulations exhibit the advantages of multi-dimensional intervention. Ginsenoside Rb2 enhances the assembly of the Atg12-Atg5 conjugate through a mammalian target of rapamycin (mTOR)-independent pathway,[23] while capsaicin activates the CaMKKβ-AMPK signaling axis via the TRPV1 calcium ion channel.[102] This multi-target characteristic enables the components of TCM formulations to simultaneously regulate the initiation, elongation, and termination stages of autophagy. In addition, certain components such as resveratrol can also selectively remove dysfunctional mitochondria through SIRT1-mediated mitophagy, blocking the excessive production of ROS at the source. The relevant active ingredients of TCM and their mechanisms of action are shown in Table 6.

Inhibiting Hepatocyte Apoptosis

Precise regulation of autophagy activity directly affects the fate of hepatocytes, ie, whether they survive or undergo programmed cell death. It has been found that apoptosis is the most clearly defined and widely studied form of hepatocyte death in the MAFLD process.[103] Apoptosis is a form of programmed cell death which occurs through the regulation of genes and their products in the cell. Hepatocyte apoptosis is usually induced by lipotoxic substances and causes hepatocyte injury through sublethal and lethal stress effects, inducing secondary liver injuries such as liver IR, inflammatory responses,

Table 5 Summary of Experimental Studies on the Effects of Active Components of Chinese Medicines on MAFLD by Alleviating Endoplasmic Reticulum Stress

Active Ingredient	Source	Pharmacological Model	Pharmacological Mechanism	Reference
Betulinic acid	*Betula pubescens*	Mice fed an HFD and MCD diet	Activates FXR; Inhibits PERK → ↓EIF2α/ATF4/CHOP → ↓ER stress	[96]
Resveratrol	Knotweed, grapes	Rats fed an HFD	Activates SIRT1 → ↓ER stress	[97]
Catalpol	*Rehmannia* root	Mice fed an HFD	Inhibits ER stress signature proteins → ↓ER stress; ↓Hepatocyte apoptosis; ↓ALT/AST/TG/TC	[98]

Note: ↑ indicates upward, promotion, or increase; ↓ indicates downward adjustment, suppression, or reduction.

Table 6 Summary of Experimental Studies on the Effects of Active Components of Traditional Chinese Medicine on MAFLD by Regulating Hepatocyte Autophagy

Active Ingredient	Source	Pharmacological Model	Pharmacological Mechanism	Reference
Resveratrol	Knotweed, grapes	HepG2 cells	Activates AMPK/SIRT1 → ↑Fatty acid β-oxidation → ↑Autophagy	[99]
Puerarin	*Pueraria lobata*	Mice fed an HFD	Activates AMPK → Inhibits mTOR → Activates ULK1; Activates PI3K/AKT	[100]
Ginsenoside Rb2	Ginseng	DB/DB mice	Activates AMPK/SIRT1; Inhibits mTOR → ↑Autophagy → ↓Inflammation	[23]
Capsaicin	Pepper	HepG2 cells	Activates TRPV1 → ↑Autophagy-associated proteins → ↓Inflammation	[102]
Bergamot polyphenols	Bergamot	Rat fed a cafeteria diet (CAF)	↑LC3/Beclin1; ↓SQSTM1/p62 → ↑Autophagy	[101]

Note: ↑ indicates upward, promotion, or increase; ↓ indicates downward adjustment, suppression, or reduction.

and fibrosis and promoting the development of MAFLD.[104] The active ingredients of Tuckahoe,[105] *Atractylodes* rhizome,[106] and *Cordyceps* flower[107] have been confirmed to be involved in inhibiting the hepatocyte apoptosis pathway and thereby slowing down the progression of MAFLD. Considering the complexity of the apoptosis signaling network, the components of TCM formulations exhibit the advantages of spatiotemporal-specific regulation. LBP are the main active components of *Lycium barbarum*. LBP alleviate oxidative stress in MCD diet-fed mice by downregulating NF-κB expression, blocking inflammation, and inhibiting liver fibrosis, thereby inhibiting hepatocyte apoptosis.[75] Gastrodia ethanol extract can significantly reduce TG and TC levels in serum, upregulate AMPK levels in liver and muscle, improve dyslipidemia, hypertension, IR, and vascular endothelial function impairment in rats fed HFD, upregulate the expression of anti-apoptotic factors, inhibit the expression of Bax protein, and thereby inhibit hepatocyte apoptosis.[108] The relevant active ingredients of TCM and their mechanisms of action are shown in Table 7.

Table 7 Summary of Experimental Studies on the Effect of Active Components of Chinese Medicine on MAFLD by Inhibiting Hepatocyte Apoptosis

Active Ingredient	Source	Pharmacological Model	Pharmacological Mechanism	Reference
Pachymaran	Tuckahoe	Mice fed an HFD	Activates PARP-1 → ↑Intestinal barrier	[105]
Atractylosin	*Atractylodes* rhizome	Mice fed an HFD	↓MDA/ROS; ↓GSH depletion → ↓Apoptosis	[106]
Cordyceps flower polysaccharide	*Cordyceps* flower	Fibrotic mice treated with CCl_4	Inhibits TNF-α → ↓Inflammation/Apoptosis; ↓ALT/AST	[107]
LBP	Wolfberry	Mice fed an MCD	Inhibits NF-κB/NLRP3 → ↓Inflammation/Oxidative stress/Fibrosis/Apoptosis; ↓ALT/AST	[75]
Gastrodia ethanol extract	*Gastrodia elata*	Rats fed a cafeteria diet (CAF)	Activates AMPK → ↑Bcl-2→↓Bax → ↓Apoptosis; ↓TG/TC	[108]

Note: ↑ indicates upward, promotion, or increase; ↓ indicates downward adjustment, suppression, or reduction.

Improving Mitochondrial Dysfunction

The inhibition of apoptosis signals is closely related to stabilization of the mitochondrial membrane potential, and the two work together to maintain homeostasis of cellular energy metabolism. At present, the "multiple shock" theory is widely used to explain the pathogenesis of MAFLD, wherein dysfunction of liver mitochondria plays an important role.[109] Elevated serum retinol-binding protein 4 levels can cause mitochondrial dysfunction and steatosis in the liver. Abnormal mitochondrial fatty acid oxidation, oxidative stress, or abnormal autophagy can induce liver inflammation and liver cell death, leading to the occurrence of MAFLD.[110] Therefore, improving mitochondrial dysfunction is an effective approach to slow down the occurrence and development of MAFLD. TCM active ingredients as ACPs,[45] quercetin,[111] icariin,[107] and puerarin[100] have been shown to play roles in the treatment of MAFLD by improving mitochondrial dysfunction. *Sagittaria sagittifolia* polysaccharide can improve lipid metabolism disorder and oxidative stress in MAFLD mice, and can also significantly improve mitochondrial damage and restore mitochondrial adenosine triphosphate (ATP) content.[68] The relevant active ingredients of TCM and their mechanisms of action are shown in Table 8.

Improving Intestinal Flora Imbalance

In addition to its regulatory effects within the liver, the restoration of mitochondrial function also indirectly affects the ecological balance of the gut microbiota through the gut-liver axis. The gut microbiota has been recognized as a key factor in the development of MAFLD. Imbalance of the intestinal flora affects the integrity of the intestinal mucosal barrier, triggers inflammation, produces bacterial metabolites, affects liver lipid metabolism and accelerates the occurrence and development of MAFLD.[112] Therefore, intestinal microbiome-targeting therapeutic strategies for MAFLD hold much value.[113] For repair of the intestinal barrier function, the synergistic effects of multiple components is particularly remarkable. Luteolin enhances tight junctions by upregulating the expression of zonula occludens 1 (ZO-1).[114] BBR reduces bacterial translocation by activating the AMPK-occludin (OCLN) signaling axis, and its effect of inhibiting the entry of endotoxins into the liver leads to a 58% decrease in the serum LPS level.[115] Artemisia polysaccharide, on the other hand, promotes the secretion of mucin by goblet cells through the IL-22/signal transducer and activator of transcription 3 (STAT3) pathway, forming a dual physical and chemical barrier.[116] In the context of metabolism-immunity regulation, components of TCM break the association between inflammation and gut microbiota imbalance through multi-target intervention. Jade bamboo polysaccharides regulates the GPR43 receptor to balance the proportion of Th17/Treg cells.[117] Oleanolic acid (OA) improves the enterohepatic circulation of bile acids through the FXR-FGF15 axis.[118] This multi-level mode of action enables compound preparations such as Qingrequzhuo capsule to simultaneously

Table 8 Summary of Experimental Studies on the Effect of Active Ingredients of Chinese Medicine on MAFLD by Improving Mitochondrial Dysfunction

Active Ingredient	Source	Pharmacological Model	Pharmacological Mechanism	Reference
ACPs	Coniferous tree	Mice fed an HFD	Inhibits UCP2 → ↑Mitochondrial coupling efficiency → ↑Fatty acid β-oxidation → ↓Lipid accumulation	[45]
Quercetin	Raspberry, ginkgo	Mice fed an HFD	Activates Nrf2 → ↓ROS → ↑Mitochondrial membrane potential → ↑ATP synthesis	[111]
Icariin	*Epimedium*	Mice fed an HFD	Activates Nrf2 → ↑xCT/GPX4 → ↓Lipid peroxidation → ↓Ferroptosis; Inhibits Caspase-3 → ↓Apoptosis	[107]
Puerarin	*Pueraria lobata*	Mice fed an HFD	Inhibits NF-κB → ↓TNF-α → ↓ROS → ↑Mitochondrial biogenesis	[100]
Sagittaria sagittifolia polysaccharide	*Sagittaria sagittifolia*	Mice fed an HFD	Activates Nrf2/HO-1 → ↓ROS → ↑Mitochondrial respiration → ↓Oxidative stress	[68]

Note: ↑ indicates upward, promotion, or increase; ↓ indicates downward adjustment, suppression, or reduction.

correct gut microbiota dysbiosis, alleviate gut-derived inflammation, and improve lipid metabolism disorders. In addition, relevant studies have shown that the bioactive components of TCM drugs such as Walnut green husk polysaccharides (WGHP),[119] *Ganoderma lucidum* mycelium polysaccharides,[120] ferulic acid (FA),[106] MP-A,[54] Qingrequzhuo capsule,[121] can improve the imbalance of the gut microbiota by improving the composition ratio of the gut microbiota. For instance, resveratrol alleviates the ecological imbalance of gut microbes, increases the abundance of Ruminococcaceae and Lachnospiraceae, reduces the abundance of Desulfovibrio (a class of anaerobic bacteria that reduce sulfate to produce H_2S), reduces bacterial invasion and translocates, and thereby regulates the endocannabinoid system. It can maintains intestinal barrier integrity, inhibit intestinal inflammation, and improve intestinal flora disorders.[122] The relevant active ingredients of TCM and their mechanisms of action are shown in Table 9.

Table 9 Summary of Experimental Studies on the Effects of Active Ingredients of Chinese Medicine on MAFLD by Improving Intestinal Flora Imbalance

Active Ingredient	Source	Pharmacological Model	Pharmacological Mechanism	Reference
WGHP	Walnut	Rats fed an HFD	↑SCFAs → ↓Dysbacteria	[119]
Ganoderma lucidum mycelium polysaccharide	Reishi	Rats fed an HFD	Inhibits Firmicutes/Bacteroidota → ↑Cecal flora richness → ↓Dysbacteria	[120]
Luteolin	Mignonette	Rats fed an HFD	↑Bacterial species → ↓Intestinal permeability → ↓Dysbacteria; Inhibits TLR4/NF-κB → ↓Inflammation	[114]
BBR	*Coptis chinensis*	Mice fed an HFD	Inhibits Bifidobacterium/Bacteroidota/Firmicutes → ↓Dysbacteria → ↓IR	[115]
Artemisia polysaccharide	*Artemisia* seed	Mice fed an HFD	Inhibits Proteus/AF12/Helicobacter pylori → ↓Dysbacteria	[116]
Jade bamboo polysaccharide	Jade bamboo	Rats fed an HFD	Inhibits SREBP1/FABP4/FAS → ↓Lipogenesis; Inhibits Fusobacterium/Enterococcus/Lactococcus/Sutterella → ↓Dysbacteria	[117]
MP-A	Mussel	Rats fed an HFD	Inhibits LPS-TLR4-NF-κB → ↓Inflammation; Inhibits PPARγ/SREBP-1c → ↓Lipogenesis → ↓Dysbacteria	[54]
FA	Cinnamon	Mice fed with HFD	↑SCFAs → ↓Inflammation/Dysbacteria	[106]
OA	Privet fruit	Rats fed an HFD	Inhibits Bacteroidota/Firmicutes → ↓Dysbacteria	[118]
Qingrequzhuo capsule	Mulberry bark, Coptis Fructus, *Poncirus aurantii*, Cicada, Alisma, safflower, Poria, Rhubarb, Achyranthes achyranthes, yam	Rats fed an HFD	Inhibits TLR4/NF-κB → ↓IL-6/IL-8/Inflammation; ↑Dubosiella/Lachnospiaceae → ↓LPS/Dysbacteria	[121]
Resveratrol	Knotweed, grapes	Rats fed an HFD	↑Ruminococcaceae/Lachnospiraceae; ↓Desulfovibrio → ↓Dysbacteria	[122]
Si miao formula	Atractylodes, Achyranthes, Yellow cedar, Coix seed	Mice fed a high-fat, high-sucrose diet	Inhibits IL-1β/NLRP3 → ↓Inflammation; ↑Akkermansia muciniphila → ↓Dysbacteria	[123]

Note: ↑ indicates upward, promotion, or increase; ↓ indicates downward adjustment, suppression, or reduction.

https://doi.org/10.2147/DDDT.S514498

Discussion

MAFLD has become an important cause of chronic liver disease worldwide. However, unless patients undergo specific tests to identify MAFLD, they remain unaware of the disease until the condition becomes severe or irreversible liver damage occurs.[124] This study elucidates how the active ingredients of TCM formulations combat MAFLD through a multi-dimensional regulatory network encompassing lipid metabolism, oxidative stress, inflammation, and gut-liver crosstalk. Specifically, we attempted to identify the pharmacological models and mechanisms of action provided in the existing literature, and thereby reveal the common bioactive components in numerous TCM ingredients that show therapeutic effects on MAFLD. The specific pathways and targets are shown in Figure 3. An inductive summary based on the chemical structures and related targets is shown in Table 10.

This study systematically constructed the first cross-scale regulatory network of the active ingredients of TCM formulations for the treatment of MAFLD. Based on the screening of the dynamic target population, a new "mechanism-oriented and spatiotemporal optimized" paradigm of TCM compound design has been proposed. However, the preclinical studies cited in this review had the following common limitations: (1) Male animals were used in 89% of the studies, and

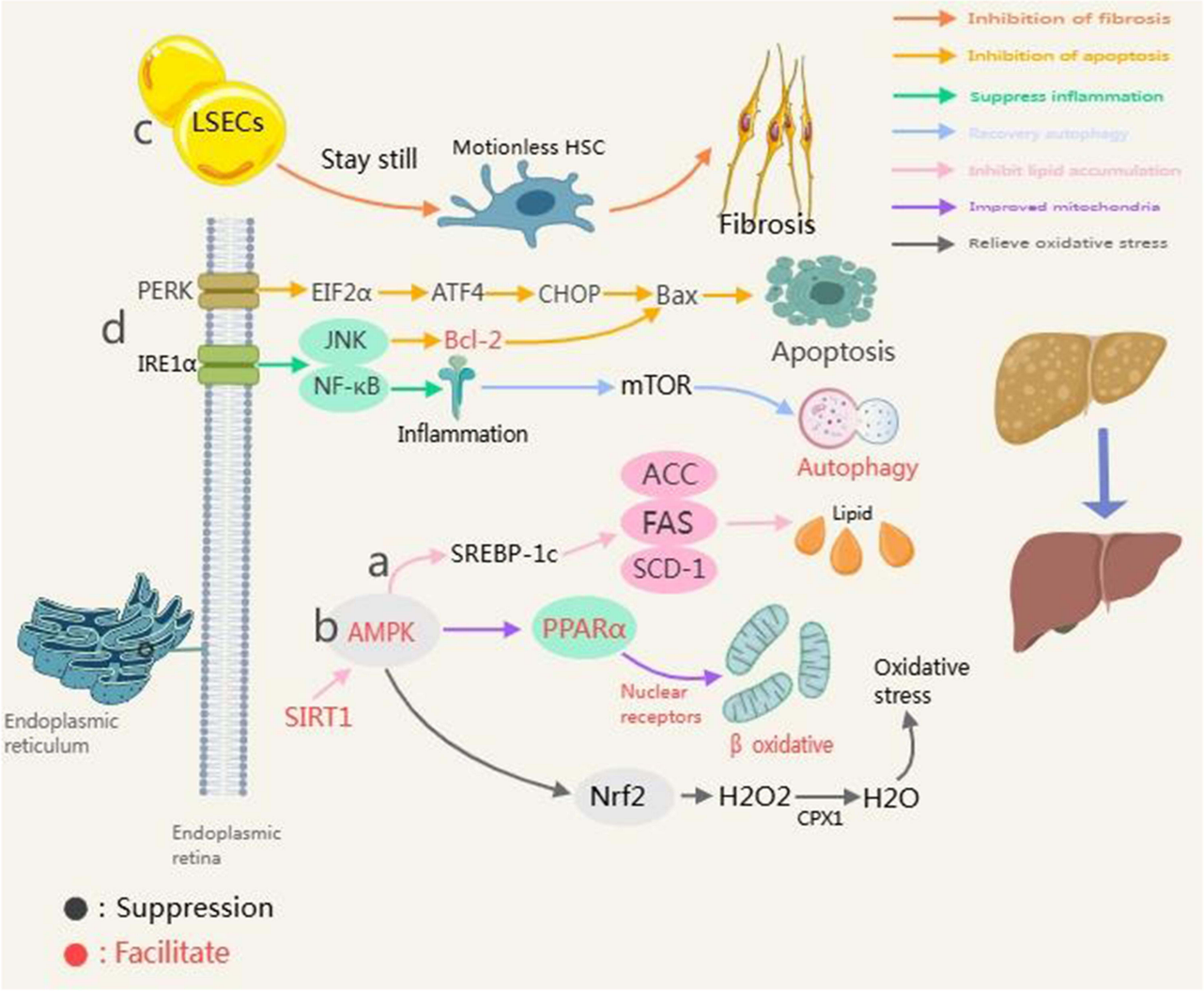

Figure 3 Mechanism of action of Chinese medicine active ingredients in treatment of MAFLD. Core early intervention targets: (a) SREBP-1c/ACC/FAS/SCD-1, reduce lipid accumulation at the source, and block the subsequent triggering of oxidative stress and fibrosis. (b) AMPK, activating AMPK can achieve dual regulation:1.Inhibit lipid synthesis (by phosphorylating ACC and SREBP-1c).2.Promote autophagy (the LC3 marker increases → clear lipids and damaged proteins). (c) LSECs-HSC, if the inactivation of liver sinusoidal endothelial cells (LSECs) is the initial trigger for the activation of hepatic stellate cells (HSCs), restoring the function of LSECs can fundamentally prevent the initiation of fibrosis. (d) IRE1α/PERK/Nrf2, alleviate the mitochondrial dysfunction and oxidative damage caused by lipid accumulation. Priority ranking: SREBP-1c/ACC/FAS>AMPK>LSECs-HSC>IRE1α/PERK/Nrf2>Bcl-2.

 https://doi.org/10.2147/DDDT.S514498

Table 10 Synergistic Targeting Analysis of Compound Classification in the Nonlinear Pathogenesis of MAFLD

Compound Class	Representative Components	Core Target Groups	Synergistic Mechanisms	Corresponding Nonlinear Pathogenesis of MAFLD
Flavonoids	Quercetin, baicalein	AMPKα2 Thr172, Nrf2, NLRP3	Causes activation of lipid oxidation (AMPK) and suppression of inflammation (NLRP3), blocks the vicious cycle of lipid toxicity-inflammation	Metabolic dysregulation amplifies inflammatory responses
Alkaloids	Berberine, matrine	PCSK9, LXRα, SIRT1	Inhibits hepatic lipid synthesis (LXRα) while activating the gut FXR pathway for gut-liver axis metabolic synergy	Bidirectional interactions between gut microbiota disorders and liver lipid deposition
Polysaccharides	*Ganoderma lucidum* polysaccharides, *Lycium barbarum* polysaccharides	TLR4/MyD88, PPARγ	Reshapes butyrate rhythm (TLR4) and enhances insulin sensitivity (PPARγ) through cross-organ coordination	Gut leakage and insulin resistance jointly promote liver damage
Terpenoids	Ursolic acid, tanshinone IIA	LXRα, CPT1A, GPX4	Enhances mitochondrial β-oxidation (CPT1A) and inhibits ferroptosis (GPX4), balances metabolic flux and cytoprotection	Dynamic imbalance between energy overload and oxidative damage
Phenolic Acids	Chlorogenic acid, resveratrol	ALKBH5 m^6A, SIRT1/PPARα	Modulates the RNA epitranscriptome (ALKBH5) and circadian metabolic rhythms (SIRT1), synchronizes gene–environment interactions	Synergistic roles of epigenetic modifications and metabolic oscillations

sex-related differences were not evaluated. (2) The methods of random grouping were not specified in 62% of the studies. (3) Only 12% of the studies conducted a blinded assessment of pathological endpoints, potentially affecting the generalizability of the conclusions. (4) Extrapolations of the findings of animal experimental results to humans are limited by the physiological and pathological differences between animals and humans, the variations in drug metabolism and response, as well as the inability of animal models to fully mimic the complex environmental and lifestyle factors involved in human diseases. Nevertheless, to maintain the integrity of the evidence, we have retained all the studies that met the inclusion criteria.

While the multi-target therapeutic effects of TCM ingredients offer advantages in MAFLD management, their potential hepatotoxicity and herb-drug interactions require rigorous evaluation. For instance, long-term administration of berberine (>500 mg/day) may alter CYP450 enzyme activity, and high-dose resveratrol supplementation (≥1 g/day) has been associated with mitochondrial membrane destabilization in hepatocytes. However, some of the compounds described in this paper have been successfully tested or evaluated in humans. For example, recent clinical evidence from a meta-analysis of 26 randomized trials (n = 2375) demonstrated that silymarin, a hepatoprotective botanical extract, significantly improved hepatic steatosis (OR = 3.25), reduced serum ALT/AST levels (SMD = −12.39/-10.97), and ameliorated lipid profiles in MAFLD patients, aligning with the multi-target therapeutic strategy proposed in this review.[125] The crux of the matter is that the nonlinear progression of MAFLD, ie, the mutual amplification of metabolic dysfunction (AMPK suppression), oxidative damage (excessive production of ROS), and inflammation (activation of NLRP3/NF-κB), is driven by the interactions among these signaling pathways. The compound classification framework (Table 10) shows that flavonoids, alkaloids, and polysaccharides achieve synergistic effects by simultaneously targeting AMPK-mediated lipid oxidation, NLRP3-driven inflammation, and insulin sensitivity enhanced by PPARγ. This therapeutic breadth is unparalleled by single-target drugs such as vitamin E or pioglitazone. Therefore, in the future, multicenter trials can be designed to validate the synergistic effects of different classes of components. For example, combining quercetin with LBP can simultaneously improve hepatic steatosis and gut barrier function, which are key indicators for reversing MAFLD. Such combinations can also address the nonlinear characteristics of MAFLD by simultaneously inhibiting oxidative stress and interrupting the crosstalk between metabolism and inflammation. In addition, compound classes that have been proven to modulate the gut-liver axis (eg, polysaccharides such as

Ganoderma lucidum polysaccharides and alkaloids like berberine) can be preferentially selected to prepare stable oral formulations for the development of standardized formulations. By jointly targeting NLRP3, PPARγ, etc., the linear progression of the AMPK-oxidative stress-inflammation axis can be broken, and the transition from various stages to an uncontrollable stage can be basically prevented.

Under the current trend of combination therapy, clarifying the mechanisms of action of different active ingredients can help address the challenges of patient compliance through sustained-release technologies, providing a practical alternative to lifestyle interventions, since 80% of patients are unable to adhere to lifestyle interventions for more than six months. Although lifestyle modification remains the cornerstone of MAFLD management, the multi-target adaptability and formulation flexibility of TCM make it a viable option for patients who experience difficulty in adhering to dietary control. By focusing on reproducible formulation engineering and clinically relevant endpoints, this field can transition from empirical practice to evidence-based precision therapy, ultimately achieving the integration of traditional wisdom and modern medicine.

Abbreviations

BA, Betulinic, acid; BiP, Binding, immunoglobulin, protein; ER, Endoplasmic, reticulum; ERS, Endoplasmic, reticulum, stress; FFA, Free, fatty, acids; FXR, Farnesoid, X, receptor; GA, Glycyrrhizic, acid; HCC, Hepatocellular, carcinoma; HFD, High-fat, diets; IR, Insulin, resistance; JNK, Jun, N-terminal, kinase; LBP, Lycium, barbarum, polysaccharides; LDL, Low-density, lipoprotein; LXR, Liver, X, receptor; MAFLD, Metabolic, dysfunction-associated, fatty, liver, disease; MCD, Methionine-choline, deficient; OA, Oleanolic, acid; ROS, Reactive, oxygen, species; SOD, Superoxide, dismutase; SREBP, Sterol, regulatory, element-binding, protein; TC, Total, cholesterol; TCM, Traditional, Chinese, medicine; TGP, Total, glucosides, of, peony; UPR, Unfolded, protein, response.

Acknowledgments

We are grateful to the sponsors of the Fund.

Author Contributions

All authors made significant contributions to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors also participated in drafting, revising, or critically reviewing the article; gave final approval for the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by National Key Research and Development Plan Project (Fund No.: 2023YFC3606203), Shandong Taishan Scholars Project Special Fund Project (Fund No.: ts201712097), and Shandong Medicine and Health Science and Technology Youth Project (Fund No.: 202303031041).

Disclosure

The authors report no conflicts of interest in this work.

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