



Review Article

The Role of Hepatic SIRT1: From Metabolic Regulation to Immune Modulation and Multi-target Therapeutic Strategies

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD), the most common chronic liver disorder worldwide, results from multidimensional network dysregulation involving lipid metabolism imbalance, insulin resistance, oxidative stress, chronic inflammation, and gut-liver axis disruption. Silent information regulator 1 (SIRT1), an NAD⁺-dependent deacetylase, functions as a central regulator of metabolic homeostasis and a key mediator in immune microenvironment remodeling and inter-organ communication. This review systematically describes the multi-target mechanisms of SIRT1 in MASLD pathogenesis through its regulation of critical factors, including peroxisome proliferator-activated receptor gamma coactivator 1- α , Forkhead Box O, and nuclear factor kappa-light-chain-enhancer of activated B cells, which govern hepatocyte lipid remodeling, mitochondrial quality control, autophagy-endoplasmic reticulum stress balance, and Kupffer cell/T cell polarization. This work introduces, for the first time, the concept that SIRT1 mediates systemic regulation of MASLD *via* coordinated "metabolism-inflammation-organ axis" interactions. Recent studies indicate that natural compounds (e.g., resveratrol, curcumin) improve gut-liver barrier function through microbiota-SIRT1 interactions, while synthetic activators (SRT1720) and NAD⁺ precursors (NMN) enhance hepatocyte antioxidant capacity and fatty acid β -oxidation. This innovative analysis highlights the spatiotemporal specificity of various SIRT1 activators, emphasizing that tissue-selective delivery and dynamic dosage optimization are crucial for overcoming clinical translation challenges. By integrating mechanistic and translational insights, this review provides a novel foundation for

precision intervention strategies targeting SIRT1 network reprogramming.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent chronic liver condition closely linked to metabolic abnormalities. Recent statistics report a global prevalence of 32.40% and an annual incidence rate of 4.69%.¹ Its incidence has steadily increased across all age groups over the past few years, contributing significantly to the global healthcare burden.² MASLD is primarily characterized by abnormal lipid accumulation in hepatocytes, typically presenting as simple steatosis. Under prolonged metabolic stress, it may progress to metabolic-associated steatohepatitis (MASH), liver fibrosis, cirrhosis, and hepatocellular carcinoma, which are among the leading causes of end-stage liver disease and liver transplantation.³

The approval of Resmetirom represents a major advancement in MASLD treatment,⁴ offering a targeted therapy for patients with progressive MASH and moderate-to-severe liver fibrosis, thereby addressing a longstanding therapeutic gap.^{5,6} However, its clinical utility remains limited, as it does not address early-stage disease. Patients with simple steatosis who have not yet progressed to MASH lack approved pharmacological options, and current clinical management primarily depends on lifestyle modification, which is often limited by poor adherence and inconsistent therapeutic outcomes.⁷ Therefore, identifying targeted, mechanism-based therapies for various stages of MASLD remains a key priority.⁸

MASLD pathogenesis involves complex, multifactorial processes characterized by the dysregulation of multiple interlinked systems and signaling pathways.⁹ Insulin resistance serves as an early pathogenic driver,¹⁰ promoting increased hepatic uptake of free fatty acids (FFAs) and activation of *de novo* lipogenesis, resulting in excess triglyceride accumula-

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tion. This chronic lipid burden impairs mitochondrial function and elevates reactive oxygen species (ROS) levels,¹¹ causing oxidative stress and hepatocellular injury.¹² Moreover, lipotoxicity, endotoxin translocation, and chronic low-grade inflammation activate Kupffer cells (KCs) and polarize immune cell populations,¹³ contributing to a persistent pro-inflammatory hepatic microenvironment. Dysbiosis of gut microbiota, altered bile acid metabolism,¹⁴ and disruption of the gut-liver barrier¹⁵ further exacerbate MASLD progression. These interconnected “metabolism–inflammation–oxidation–immune” processes define the systemic complexity of MASLD and offer multiple potential therapeutic targets.

Silent information regulator 1 (SIRT1), an NAD⁺-dependent deacetylase, has emerged as a central regulator at the interface of metabolic regulation, inflammatory signaling, and cellular defense mechanisms.¹⁶ SIRT1 is broadly expressed in metabolically active tissues¹⁷ and regulates lipid metabolism,¹⁸ mitochondrial maintenance, ROS clearance, autophagy, and immune balance by deacetylating key transcriptional regulators, including peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α), Forkhead Box O (FOXO), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and p53.¹⁹ Its expression and enzymatic activity are regulated by AMP-activated protein kinase (AMPK), the NAD⁺/NADH ratio, miRNAs, and protein-protein interactions.^{20–22} Increasing evidence suggests that SIRT1 plays a key regulatory role at several stages of MASLD pathogenesis, identifying it as a promising therapeutic target with both systemic and stage-specific applications.

Given the central role of SIRT1 in the “metabolism–inflammation–immune” signaling axis, this review systematically examines its regulatory functions in MASLD initiation and progression. The focus is on SIRT1’s roles in hepatic lipid metabolism reprogramming, insulin signaling, oxidative stress control, and intrahepatic immune regulation. Furthermore, this review summarizes current research and pharmacological developments involving natural compounds, synthetic agents, and NAD⁺ precursors as SIRT1 activators, assessing their feasibility in multi-target interventions and clinical applications. By integrating mechanistic and pharmacological insights, this work aims to establish a comprehensive theoretical framework for advancing SIRT1-based therapeutic strategies in MASLD.

Structure and regulatory mechanisms of SIRT1

SIRT1, a representative member of the mammalian sirtuin family, is classified as an NAD⁺-dependent class III histone deacetylase.¹⁶ It is widely expressed in metabolically active tissues, including the liver, heart, skeletal muscle, and adipose tissue,^{23–25} and is involved in diverse cellular processes such as metabolic homeostasis, antioxidant defense, autophagy, inflammation, and energy balance.^{26–28} In the complex pathological progression of MASLD, SIRT1 exerts effects through its structural properties and intricate regulatory mechanisms.

Structurally, SIRT1 contains a conserved catalytic core domain (□275 amino acids) located in the central region of the protein. This domain includes both the NAD⁺-binding region and the substrate recognition site, which are essential for its deacetylation function.^{29,30} The N- and C-terminal regions are more flexible, facilitating interactions with regulatory proteins, controlling subcellular localization, and modulating enzymatic activity. SIRT1 targets both histone and non-histone substrates, including histones (e.g., H3K9, H4K16³¹) and transcriptional regulators such as p53,³² FOXO1/3a,³³ PGC-1 α ,³⁴ LKB1,³⁵ and NF- κ B p65,³⁶ thereby contributing to

epigenetic regulation and broader cellular functions.

At the regulatory level, SIRT1 expression is influenced by transcriptional, epigenetic, post-transcriptional, and metabolic mechanisms.^{27,37} Transcriptionally, regulators such as c-Myc,³⁸ E2F1,³⁹ and p53⁴⁰ can either positively or negatively modulate SIRT1 promoter activity. Epigenetic control involves histone acetylation and DNA methylation, which influence transcriptional accessibility.^{41,42} Post-transcriptionally, several miRNAs, including miR-34a,⁴³ miR-132,⁴⁴ and miR-217,⁴⁵ target the 3′ untranslated region of SIRT1 mRNA and inhibit translation. In metabolic disorders and chronic inflammatory states, hepatic miR-34a levels are frequently elevated, often coinciding with reduced SIRT1 expression.⁴⁶

The enzymatic activity of SIRT1 is primarily regulated by the NAD⁺/NADH ratio, a key indicator of intracellular energy status.⁴⁷ AMPK indirectly promotes SIRT1 activation by up-regulating nicotinamide phosphoribosyltransferase, thereby increasing NAD⁺ biosynthesis.⁴⁸ Conditions such as high-fat diet exposure or oxidative stress result in NAD⁺ depletion and reduced SIRT1 activity. SIRT1 function is also modulated through protein-protein interactions: DBC1 inhibits SIRT1 activity via complex formation,^{30,49} whereas AROS and SENP1 interact with SIRT1 to enhance its activity, expanding the spectrum of functional regulation.^{50,51}

Overall, SIRT1 functions as a key metabolic sensor and epigenetic regulator, with both expression and enzymatic activity finely tuned by internal and external cellular signals.⁵² In the liver, SIRT1 plays a central role at the intersection of lipid metabolism, insulin sensitivity, and inflammatory signaling, coordinating metabolic adaptation through a network of regulatory pathways.^{23,53,54} A thorough understanding of its structural framework and regulatory mechanisms is essential for advancing targeted therapeutic strategies aimed at SIRT1 activation in MASLD.

Multifactorial pathogenesis of MASLD

MASLD is a chronic liver condition primarily driven by metabolic dysregulation, sustained by inflammatory responses, and exacerbated by gut-liver axis dysfunction.^{55,56} Its pathogenesis is highly complex, involving the interplay of factors including lipid metabolism disorders,⁵⁷ insulin resistance,¹⁰ oxidative stress,⁵⁸ immune activation,¹³ and gut microbiota dysbiosis.⁵⁹ This multifactorial nature is characterized by pronounced heterogeneity and systemic network interactions.

Insulin resistance, a hallmark of early-stage MASLD, impairs insulin-mediated inhibition of adipose tissue lipolysis, resulting in elevated circulating FFAs.⁶⁰ These FFAs are transported to the liver, contributing to triglyceride accumulation.⁶¹ Concurrently, persistent activation of the sterol regulatory element-binding protein 1c (SREBP-1c) pathway in hepatocytes promotes *de novo* lipogenesis, further increasing lipid deposition.^{62,63} This creates a lipotoxic environment due to excessive lipid input and synthesis. Continuous lipid accumulation impairs mitochondrial function and elevates ROS production,⁶⁴ leading to lipid peroxidation, DNA damage, and protein denaturation, collectively initiating oxidative stress, inflammatory signaling, and hepatocellular injury.¹²

As lipotoxic stress persists, innate immune responses within the liver are activated.¹³ KCs release pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-6, which recruit monocytes and drive macrophage polarization.⁶⁵ This establishes a persistent pro-inflammatory hepatic microenvironment, further exacerbating liver injury. Accumulated ROS also activate the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome, initiating caspase-1-mediated py-

roptosis and amplifying immune-mediated hepatocyte injury.^{66,67} Furthermore, oxidative stress disrupts mitochondrial membrane potential, impairs autophagy, and induces apoptosis, contributing to progressive liver damage.⁶⁸

Beyond hepatic processes, alterations in gut microbiota composition and impairment of the gut-liver barrier are key contributors to MASLD pathogenesis.^{57,69} Disease progression is associated with reduced microbial diversity and increased abundance of harmful taxa such as Proteobacteria and Enterobacteriaceae.⁷⁰ These changes reduce short-chain fatty acid (SCFA) production and increase secondary bile acid formation, both of which compromise gut barrier integrity.⁷¹ As a result, endotoxins such as lipopolysaccharide (LPS) translocate across the epithelial barrier and reach the liver via the portal circulation. LPS activates Toll-like receptors (TLRs), particularly TLR4,⁷² triggering immune responses and cytokine release. At the same time, bile acid signaling pathways, including the farnesoid X receptor (FXR)-FGF15 and TGR5-glucagon-like peptide-1 (GLP-1) axes, are disrupted, further promoting hepatic lipid accumulation and immune dysregulation.⁷³ These processes form a self-reinforcing loop within the “gut-liver inflammation axis”, driving disease progression.⁷⁴

Fibroblast growth factor 21 (FGF21) also contributes to MASLD pathogenesis. FGF21 interacts with SIRT1 to promote fatty acid oxidation, improve insulin sensitivity, and reduce hepatic inflammation, supporting metabolic regulation.⁷⁵ However, in the context of gut microbiota imbalance and barrier dysfunction, the metabolic regulatory function of FGF21 is compromised. Through the FGF21-SIRT1 axis, FGF21 may shift from a protective to a dysregulatory role, exacerbating hepatic lipid accumulation and metabolic imbalance in advanced disease stages.⁷⁶

MASLD arises from the integrated dysregulation of multiple systemic networks. Lipid metabolism imbalance contributes to energy excess, insulin resistance worsens metabolic disruption, immune activation drives cellular injury, and gut-liver axis dysfunction impairs immune and metabolic stability. These combined factors drive progressive liver damage, as illustrated in Figure 1. Within this pathophysiological context, SIRT1 acts as a central regulator at the interface of metabolic, inflammatory, and oxidative processes, contributing to hepatic lipid reprogramming, insulin sensitivity, ROS management, autophagy maintenance, and gut-liver barrier protection. The following sections will examine the multifaceted regulatory roles of SIRT1 in MASLD development and progression.

Mechanistic roles of SIRT1 in MASLD

Cell type specificity: A critical layer of complexity

The liver is a heterogeneous organ composed of both parenchymal and non-parenchymal cells. Hepatocytes represent the majority of liver mass, while non-parenchymal cells include KCs, hepatic stellate cells (HSCs), liver sinusoidal endothelial cells, and infiltrating immune cells such as lymphocytes and neutrophils.^{77,78} SIRT1 exhibits distinct expression levels, subcellular distributions, downstream targets, and functional effects across these different liver cell types. This cell type specificity represents a critical factor in understanding SIRT1's diverse roles in MASLD and explains why systemic SIRT1-directed interventions may yield divergent or inconsistent findings.⁷⁹

Generalizing the effects of “hepatic SIRT1” without distinguishing among cell types—or extrapolating hepatocyte-specific observations to the entire liver—risks producing

oversimplified or inaccurate interpretations. The pathophysiological significance of SIRT1 depends on the specific cellular context, particularly in a complex, multi-cellular disease such as MASLD. A detailed analysis of SIRT1's functions across liver cell populations is therefore essential to understanding its regulatory mechanisms in MASLD pathogenesis.

The following section examines SIRT1 activity in key hepatic cell types, drawing on evidence from cell-specific knockout and overexpression models, and highlights its distinct contributions to the cellular and molecular landscape of MASLD.

Lipid metabolism regulation

The liver is the central organ of lipid metabolism, and its metabolic function plays a key role in MASLD development and progression. SIRT1, an NAD⁺-dependent class III histone deacetylase, regulates hepatic lipid metabolism through deacetylation of multiple transcription factors and metabolic enzymes, exerting a bidirectional effect on lipid homeostasis by inhibiting fat synthesis and promoting fatty acid oxidation.⁸⁰

In lipid synthesis, SIRT1 deacetylates SREBP-1c in hepatocytes, reducing its nuclear translocation and transcriptional activity. This downregulates lipogenic enzymes such as fatty acid synthase and acetyl-CoA carboxylase, limiting fatty acid and triglyceride production.^{81–83} SIRT1 also negatively regulates glycerol-3-phosphate acyltransferase, further inhibiting triglyceride synthesis.^{19,84} Hepatocyte-specific SIRT1 knockout mice display liver steatosis, triglyceride accumulation, and increased *de novo* lipogenesis, even under standard dietary conditions, accompanied by SREBP-1c activation and impaired PGC-1 α /peroxisome proliferator-activated receptor α (PPAR α) signaling.^{85,86} Conversely, hepatocyte-specific SIRT1 overexpression reduces high-fat diet-induced hepatic lipid accumulation, suggesting a protective role in hepatocytes.

Regarding fatty acid oxidation, SIRT1 activates PPAR α and its coactivator PGC-1 α through deacetylation, facilitating mitochondrial β -oxidation.^{34,87} PGC-1 α increases expression of carnitine palmitoyltransferase 1A and acyl-CoA oxidase 1, supporting fatty acid transport and oxidation within mitochondria and reducing hepatic lipid droplet accumulation.^{88,89} Under energy-deprived conditions, such as fasting, SIRT1 activity is upregulated, promoting fatty acid oxidation and ketogenesis via the PGC-1 α /PPAR α axis, thereby improving hepatic metabolic adaptability.^{90–92}

Pharmacological studies indicate that SIRT1 activators, including SRT1720, enhance PGC-1 α deacetylation and improve fatty acid oxidation efficiency. In high-fat diet-induced MASLD models, these compounds reduced hepatic lipid droplet content and triglyceride levels.⁹³ Impaired SIRT1 function decreases PPAR α activity, leading to lipid metabolism disorders, increased hepatic lipid deposition, and aggravated inflammatory responses.⁹⁴

It is important to note that SIRT1 regulation of lipid metabolism is tissue-specific and dependent on metabolic conditions.^{17,95} In non-parenchymal cells such as KCs and HSCs, SIRT1's direct role in lipid metabolism is limited; instead, it modulates inflammatory and activation states, indirectly affecting hepatocyte lipid metabolism.¹⁹ Under conditions of overnutrition or high-fat intake, hepatic SIRT1 expression is reduced, resulting in persistent activation of lipogenic signaling and impaired fatty acid oxidation, ultimately disrupting hepatic lipid homeostasis.^{19,96} Restoration of SIRT1 activity suppresses lipid synthesis, improves oxidation capacity, and reestablishes lipid clearance, supporting therapeutic strategies aimed at metabolic reprogramming in MASLD.⁹⁷

In conclusion, SIRT1 maintains lipid metabolic balance by inhibiting lipid synthesis and promoting fatty acid oxidation through the regulation of key transcriptional regulators such as SREBP-1c and PGC-1 α , along with enzymes involved in hepatic lipid metabolism.^{82,98} Its tissue-specific regulation and sensitivity to metabolic states must be considered in developing MASLD therapies. Further investigation into its involvement in lipid droplet degradation, lipophagy, and circadian regulation is needed to fully define its role within the hepatic lipid metabolic network.^{99–102}

Insulin resistance is a key pathophysiological feature of MASLD,¹⁰ and SIRT1 plays a central role in regulating insulin signaling and hepatic glucose metabolism.^{82,103} As an NAD⁺-

In hepatocytes, SIRT1 increases insulin sensitivity by activating the LKB1/AMPK pathway, improving cellular responsiveness to insulin.¹⁰⁴ It facilitates glucose uptake and suppresses hepatic gluconeogenesis. SIRT1 deacetylates and inhibits the transcription factor FOXO1,¹⁰⁵ reducing its ability to activate gluconeogenic genes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase.¹⁰⁶ This decreases hepatic glucose production and reduces hyperglycemia. Hepatocyte-specific SIRT1 knockout mice exhibit impaired glucose tolerance, decreased insulin sensitivity, and elevated HOMA-IR values, supporting a protective role of SIRT1 in hepatic glucose homeostasis.^{107,108}

Beyond direct effects on insulin signaling, SIRT1 indirectly modulates insulin sensitivity by regulating autophagy via the mTOR pathway.^{30,109} Under nutrient excess, suppressed SIRT1 expression impairs autophagic activity,⁹⁶ leading to mitochondrial dysfunction and ROS accumulation, further disrupting insulin signaling. SIRT1 activation restores autophagy by deacetylating FOXO3a and upregulating autophagy-related genes, including Atg5 and LC3-II, enhancing cellular stress adaptability and improving insulin sensitivity.^{110,111}

Preclinical data indicate that SIRT1 activators, such as resveratrol and SRT1720, improve insulin tolerance by activating the AMPK/IRS-1/Akt pathway, inhibiting FOXO1,¹¹² and downregulating phosphoenolpyruvate carboxykinase and glucose-6-phosphatase expression. These interventions ameliorate insulin resistance at both molecular and physiological levels.¹¹³

SIRT1-mediated regulation of insulin signaling is highly context-dependent. During energy deficit, fasting, or physical activity, SIRT1 activity is upregulated, supporting glucose utilization and inhibiting gluconeogenesis.^{17,114} High-glucose and high-fat environments suppress SIRT1 expression, contributing to impaired insulin signaling and MASLD progression.⁹⁶ While SIRT1 in adipose tissue significantly affects systemic insulin sensitivity, its direct role in non-parenchymal liver cells in glucose metabolism remains unclear and is likely mediated through immune and inflammatory signaling pathways.

SIRT1 regulates insulin sensitivity and glucose metabolism by targeting key signaling pathways, including AMPK/FOXO1 and IRS-1/Akt. It is essential for maintaining hepatic glucose balance and alleviating insulin resistance in MASLD. Future studies should explore the dynamic interactions among SIRT1, mTOR, autophagy, and endoplasmic reticulum (ER) stress to elucidate its regulatory functions under varying metabolic states, guiding the development of targeted interventions for early-stage MASLD-related metabolic disorders.

Inflammation and immune modulation

Chronic inflammation and immune dysregulation are central to the pathogenesis and progression of MASLD,¹¹⁵ particularly during the transition from simple steatosis to MASH.¹¹⁶ SIRT1, a key molecular regulator at the crossroads of metabolic and immune pathways, modulates immune cell function through deacetylation, affecting inflammation, autophagy, and oxidative stress responses, thereby maintaining hepatic immune homeostasis.

In KCs, SIRT1 deacetylates the NF- κ B p65 subunit, inhibiting its transcriptional activity and reducing the expression of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. This limits macrophage polarization toward the M1 pro-inflammatory phenotype.¹¹⁷ SIRT1 also activates FOXO3a, which upregulates autophagy-related genes such as Atg5 and Atg7, promoting autophagosome formation and reducing ROS levels, thereby attenuating inflammation.^{118,119} Furthermore, SIRT1 negatively regulates the NLRP3 inflammasome, suppressing pyroptosis and protecting hepatocytes from excessive immune-mediated damage.¹²⁰ In myeloid cell-specific SIRT1 knockout mice, lipid toxicity or LPS stimulation induced more severe hepatic inflammation, elevated pro-inflammatory cytokine levels, and enhanced M1 macrophage polarization, highlighting the critical role of SIRT1 in preserving immune balance.¹²¹

In T lymphocytes, SIRT1 exerts distinct regulatory effects on helper T cells (Th).^{18,122} It deacetylates STAT4, reducing its activity and inhibiting Th1 differentiation, which decreases IFN- γ production and mitigates KC activation.^{123,124}

During early-stage MASLD, SIRT1 supports anti-inflammatory responses by deacetylating and activating Th2-related transcription factors, increasing IL-10 expression.¹²⁵ As disease progresses, SIRT1 further modulates Th2 activity by downregulating their pro-fibrotic signaling.¹²⁶ In liver fibrosis models, SIRT1 activation reduces Th2-derived pro-fibrotic cytokine levels. While limited research exists on cytotoxic T cells (Tc) in MASLD, studies in other immune disorders suggest SIRT1 regulates Tc function through T cell receptor expression and deacetylation of effector proteins such as perforin and granzyme.¹²⁷

SIRT1 is also crucial for regulatory T cell (Treg) differentiation and maintenance. Through Foxp3 deacetylation, SIRT1 enhances Foxp3 stability and activity, increasing Treg numbers and improving suppressive capacity.¹²⁸ In MASLD models, SIRT1 activation elevates hepatic Treg populations and immunosuppressive cytokines such as IL-10 and TGF- β , reducing hepatic inflammation.¹²⁹

B cells contribute to hepatic immune regulation in MASLD.¹³⁰ SIRT1 deacetylates NF- κ B, inhibiting pro-inflammatory cytokines (IL-6, TNF- α) while promoting anti-inflammatory cytokines (IL-10),³⁵ limiting Th17 and Tc activation and supporting overall immune balance.¹³¹

In neutrophils, SIRT1 inhibits IKK β acetylation, stabilizing I κ B α and preventing NF- κ B nuclear translocation and downstream expression of chemokines such as CXCL1 and IL-8, reducing neutrophil recruitment.¹³² Inflammatory stimuli also drive HMGB1 release into the extracellular space, including ROS production and neutrophil extracellular trap (NET) formation.¹³³ Excessive NETs exacerbate hepatic inflammation in MASLD. SIRT1 may reduce NET formation by deacetylating FOXO1 and increasing the expression of the pro-apoptotic protein Bim, which destabilizes mitochondrial membranes by interacting with anti-apoptotic members of the Bcl-2 family and shortens neutrophil survival, limiting their accumulation in liver tissue.^{134,135} SIRT1 governs multiple immune-regulatory processes in MASLD through deacetylation of key molecular targets. SIRT1 limits inflammation, maintains immune tolerance, and regulates cell survival.¹³⁶ In KCs, it inhibits NF- κ B signaling; in T cells, it modulates Th1/Th2 and Treg/Th17 balance;¹³⁷ and in B cells and neutrophils, it controls cytokine expression, migration, and lifespan, collectively preserving hepatic immune homeostasis.²⁶ Despite extensive research, its functions across immune subtypes and disease stages require further investigation. Future studies should clarify intercellular signaling between immune cells and hepatocytes in early and advanced MASLD to inform SIRT1-based immune-targeted therapies.

Pyroptosis regulation

Pyroptosis is a form of inflammatory programmed cell death distinct from apoptosis. It is triggered by activation of inflammatory caspases, such as caspase-1, via inflammasomes (e.g., NLRP3), leading to the release of pro-inflammatory cytokines IL-1 β and IL-18 and resulting in membrane rupture. This causes leakage of cellular contents and a strong local inflammatory response.¹³⁸ Pyroptosis is implicated in infections, autoimmune disorders, and metabolic diseases, including MASLD.

In MASLD, pyroptosis has both pathogenic and protective roles.¹³⁹ On the pathogenic side, hepatic accumulation of FFAs, oxidative stress, and gut barrier dysfunction lead to LPS translocation, activating the NLRP3 inflammasome.¹⁴⁰ This induces hepatocyte pyroptosis via the classical pathway, releasing IL-1 β and IL-18, which recruit immune cells and activate NF- κ B signaling, amplifying pro-inflammatory mediator production and promoting progression from simple ste-

apoptosis to MASH.¹⁴¹ Cellular contents released during pyroptosis activate HSCs, increase collagen synthesis, and promote fibrosis. Elevated liver levels of the gasdermin D N-terminal fragment (GSDMD-N) correlate with disease activity scores (NAS) and fibrosis severity in MASLD patients, while *GSDMD* knockout reduces fibrosis in mice.¹⁴² Inflammatory mediators from pyroptosis also impair insulin signaling, increase insulin resistance, and upregulate lipid synthesis genes, contributing to hepatic lipid accumulation.^{143,144}

Pyroptosis can also be protective. Physiologically, it eliminates hepatocytes damaged by lipotoxicity and abnormal lipid accumulation, preventing secondary tissue injury. Low-level NLRP3 activation regulates hepatic lipid metabolism via IL-18, and its absence is associated with increased steatosis. Pyroptosis-associated signals also initiate hepatic repair and support regeneration.^{145,146} Inhibition of core pyroptotic mediators (NLRP3, caspase-1, GSDMD¹⁴⁷) improves hepatic histopathology in MASLD models, highlighting their therapeutic relevance.¹⁴⁸

SIRT1 alleviates MASLD by regulating pyroptosis. Plant sterol esters from α -linolenic acid activate SIRT1, downregulating NLRP3 and ASC expression, reducing colocalization with cleaved caspase-1, and lowering GSDMD cleavage, thereby inhibiting hepatocyte pyroptosis and slowing MASH progression in mice.¹⁴⁹ The traditional Chinese medicine formula XZTZ acts via SIRT1 to downregulate NLRP3 and GSDMD, reduce pro-inflammatory cytokines, and promote macrophage polarization from M1 to M2, improving the hepatic immune microenvironment. SIRT1 also regulates pyroptosis through the GSDME-IL-18 axis, limiting IL-18 release and disrupting inflammatory feedback loops.¹²⁰ Astragaloside, via the AMPK/SIRT1 pathway, decreases pyroptosis-related proteins (NT-GSDMD, IL-1 β) in macrophages and promotes M2 polarization, alleviating liver inflammation.¹⁵⁰ Certain natural compounds also modulate autophagy via SIRT1, improving lipid metabolism and reducing pyroptosis induced by lipid toxicity, thereby slowing MASLD progression.¹⁵¹

In summary, SIRT1 precisely regulates pyroptosis at initiation, execution, and downstream inflammatory signaling. By integrating metabolic regulation with inflammation suppression, SIRT1 represents a promising therapeutic target in MASLD and related inflammatory liver diseases. Further investigation of these pathways could provide a mechanistic foundation for developing targeted interventions.

Autophagy and ER stress alleviation

Autophagy is a critical protective mechanism against nutrient deprivation and metabolic stress, essential for maintaining hepatocyte homeostasis. SIRT1 regulates autophagic flux through multiple pathways, alleviating lipotoxic and inflammatory damage in MASLD.^{152–154}

In the classical pathway, hepatocellular SIRT1 deacetylates FOXO1¹⁰⁵ and FOXO3a,¹⁵⁵ inducing expression of autophagy-related proteins such as Atg5, Atg7, and Beclin-1, which promote autophagosome formation and maturation. Concurrently, SIRT1 activates AMPK and inhibits the mTOR pathway, releasing inhibition of autophagy and increasing clearance of lipid droplets and damaged mitochondria.^{28,30,156} Animal studies demonstrate that a high-fat diet impairs autophagic function,⁹⁶ whereas SIRT1 agonists enhance hepatic autophagy, reduce lipid peroxidation and ROS accumulation, and improve hepatocyte function.¹⁵¹

Lipophagy, a selective form of autophagy, involves the direct engulfment and degradation of cytoplasmic lipid droplets by autophagosomes. It represents a key mechanism by which hepatocytes eliminate excess triglycerides, independent of the traditional cytosolic lipase-mediated hydrolysis

pathway.¹⁵⁷ SIRT1 plays a specific role in lipophagy regulation. In MASLD, reduced SIRT1 activity leads to hyperacetylation and stabilization of PLIN2 and PLIN3, effectively “locking” lipid droplets and impairing lipophagic clearance, exacerbating triglyceride accumulation.¹⁵⁷ SIRT1-mediated deacetylation of PLINs enhances lipophagy, representing a key mechanism for alleviating hepatic steatosis.¹⁵⁸

ER stress is another important inflammatory and pro-apoptotic factor in MASLD progression.¹⁵⁹ SIRT1 alleviates ER stress by deacetylating molecules such as eIF2 α and CHOP,³² inhibiting excessive activation of the unfolded protein response,¹⁶⁰ and reducing expression of stress-related proteins including GRP78 and ATF4.³² This limits ER stress-associated hepatocyte apoptosis and inflammation. SIRT1 also regulates the IRE1 α /XBP1 axis, decreasing release of inflammatory mediators and apoptotic signals.¹⁶¹

There is extensive cross-regulation between autophagy and ER stress,¹⁶² and SIRT1 may coordinate the feedback mechanisms between these processes.¹⁶³ For example, SIRT1-mediated deacetylation of TSC2, an upstream regulator of mTOR, indirectly synchronizes ER stress levels with autophagic activity.¹⁶⁴ The NAD⁺/SIRT1 signaling pathway functions as a central node linking nutrient sensing, autophagy regulation, and ER adaptation.²⁸ Research on SIRT1's role in non-parenchymal liver cells, such as KCs and HSCs, is limited. In KCs, autophagy may affect functional polarization,¹⁶⁵ while in activated HSCs, it may sustain a pro-fibrotic phenotype.¹⁶⁶ The role of SIRT1 in these mechanisms and its overall effect on MASLD pathology remain to be fully elucidated.

SIRT1 alleviates MASLD by activating autophagy and mitigating ER stress, serving a coordinated “clear-buffer-repair” function in hepatocytes that enables adaptation to metabolic stress and limits cellular damage.¹⁹ Further studies are needed to define the temporal and mechanistic precision of SIRT1 in autophagic regulation and its integration with unfolded protein response and oxidative stress networks.

Mitochondrial homeostasis and ROS control

Mitochondrial dysfunction and excessive ROS generation are key factors in MASLD progression.^{167,168} In hepatocytes, elevated lipid load and insulin resistance increase mitochondrial β -oxidation activity, accompanied by electron leakage and respiratory chain disruption, resulting in substantial ROS production, which exacerbates lipid peroxidation, autophagic dysfunction, and pyroptosis.⁶⁴ SIRT1 serves as a central regulator of redox homeostasis, controlling ROS generation and mitochondrial quality through multiple pathways.¹⁶⁹

SIRT1 activates antioxidant transcription factors such as FOXO3a and Nrf2 via deacetylation,¹⁷⁰ upregulating enzymes including superoxide dismutase (SOD) 1/2, GSH-Px,¹⁷¹ and HO-1.¹⁷² This enhances free radical neutralization and reduces oxidative stress. SIRT1 simultaneously inhibits NF- κ B activity, lowering ROS-induced pro-inflammatory cytokine production, thereby providing bidirectional regulation of oxidative stress and inflammation.¹⁷³ Animal studies show that SIRT1 activation reduces MDA content, ROS accumulation, and mitochondrial membrane potential loss, ultimately delaying hepatocyte apoptosis.¹⁷⁴

Regarding mitochondrial homeostasis, SIRT1 regulates biogenesis and metabolic remodeling by activating PGC-1 α , enhancing mitochondrial quantity and function. PGC-1 α upregulation induces NRF1/2 and TFAM expression, supporting mtDNA replication and respiratory chain activity.¹⁷⁵ SIRT1 also regulates mitophagy via the PINK1/Parkin and BNIP3 pathways, facilitating removal of dysfunctional mitochondria.¹⁷⁶ Through deacetylation of key molecules such as p53 and LC3, SIRT1 initiates mitochondria-specific autophagy,

playing a central role in quality control.

SIRT1 also provides feedback regulation along the ROS-mitochondrial damage-autophagic dysfunction axis,^{102,177,178} reducing oxidative accumulation and repairing mitochondrial metabolic alterations, interrupting the “oxidative stress-inflammation-energy collapse” cycle in MASLD. Reduced SIRT1 activity correlates with mtDNA damage, mitochondrial fragmentation, decreased membrane potential, and impaired adenosine triphosphate synthesis, all contributing to disease progression and transition to MASH.

However, under certain conditions, SIRT1 activation may exacerbate oxidative injury depending on NAD⁺ availability, tissue microenvironment, and timing. In NAD⁺-depleted states (e.g., aging or advanced disease), SIRT1 activation consumes residual NAD⁺, impairing NAD⁺-dependent repair enzymes such as PARPs, and increasing oxidative stress.^{29,179} In chronic high-oxygen exposure or paraquat-induced injury,^{180,181} SIRT1 activation can worsen mitochondrial impairment and ROS generation by modulating apoptosis-related proteins and inhibiting Nrf2-mediated antioxidant expression.¹⁸² Its effects vary by cell type; excessive activation in KCs may reduce lipid peroxidation clearance.¹⁸³

Dose-dependent and off-target effects of SIRT1 activators must also be considered. High concentrations of resveratrol may inhibit mitochondrial complex I, while synthetic activators like SRT2104 require high doses due to poor liver targeting, increasing oxidative stress risk in extrahepatic tissues. In late-stage MASLD or end-stage heart failure, where mitochondria are severely compromised and NAD⁺ depleted, SIRT1 activation may further aggravate oxidative injury by promoting mitochondrial fission and excessive autophagy, depleting cellular energy.¹⁸⁴ Interactions with p53 and NF- κ B may also produce harmful effects, such as inhibiting p53-mediated antioxidant transcription or sustaining NF- κ B activation during severe inflammation.¹⁸⁵

SIRT1 is essential for controlling ROS production, maintaining mitochondrial function, and regulating selective autophagy. Its actions, however, are highly context-dependent, and under conditions of NAD⁺ depletion, specific cell types, dosing imbalances, or advanced disease, SIRT1 may exacerbate oxidative damage by impairing repair enzyme activity, exacerbating mitochondrial dysfunction, and weakening antioxidant responses. Future studies should clarify these context-specific mechanisms to enable safe and precise application of SIRT1-targeted therapies in metabolic liver disease.

Gut-liver axis and gut microbiota

The gut-liver axis, a fundamental physiological pathway connecting the gastrointestinal tract and liver, contributes significantly to the onset and progression of MASLD.^{57,186} Alterations in gut microbiota composition, compromised intestinal barrier integrity, and abnormal translocation of microbial metabolites allow endotoxins, such as LPS, to reach the liver *via* the portal circulation. This process activates KCs in the liver, triggering the release of pro-inflammatory cytokines, including TNF- α and IL-6, which exacerbate hepatocellular steatosis. Simultaneously, the immune balance between Th17 cells and Tregs is disrupted. The resulting increase in Th17-associated cytokine secretion promotes the onset of steatohepatitis and fibrosis.

SIRT1 contributes to the repair of intestinal barrier function by upregulating tight junction proteins, such as zonula occludens-1, through deacetylation of histone H3K9 and the transcription factor FOXO1. This mechanism reduces endotoxin translocation and inhibits activation of the hepatic TLR4/NF- κ B inflammatory signaling pathway induced by LPS from Enterobacteriaceae.^{187,188} Moreover, SIRT1 participates

in the bidirectional regulation of SCFA metabolism, particularly butyrate, which enhances intracellular NAD⁺ levels *via* G-protein-coupled receptor signaling. Elevated NAD⁺ levels activate SIRT1, which further promotes the activity of PGC-1 α and PPAR α . These factors, together with SCFAs, inhibit hepatic lipogenesis, promote fatty acid oxidation, and support the proliferation of butyrate-producing microbiota, forming a positive metabolic feedback loop.¹⁷⁰ In the presence of conditionally pathogenic bacteria, SIRT1 activation alleviates intestinal oxidative stress *via* the FOXO1-SOD2 axis. This limits the proliferation of *Enterococcus* and *Klebsiella pneumoniae*, while also inhibiting excessive growth of *Escherichia coli* through the induction of antimicrobial peptides.^{189,190} Furthermore, SIRT1 increases the transcriptional activity of FXR through deacetylation, facilitating the conversion of cholesterol to bile acids. This results in the production of deoxycholic acid, which inhibits the proliferation of pathogenic *Clostridium* species and reduces the production of deleterious microbial metabolites.^{191–193} FXR activation promotes the secretion of GLP-1 from intestinal endocrine cells, which enhances insulin release, improves insulin sensitivity, and promotes glucose metabolism.¹⁹⁴ GLP-1 also acts directly on the liver, inhibiting glycogenolysis, promoting glycogen synthesis, and regulating the expression of lipid metabolism-associated genes, thereby reducing hepatic fat accumulation and improving glucose and lipid homeostasis along the gut-liver axis.

Overall, SIRT1 establishes a multifaceted regulatory framework across the “microbiota-barrier-signaling” axes. This coordination reduces hepatic exposure to gut-derived inflammatory stimuli while simultaneously alleviating metabolic and immune stress through improved microbial homeostasis, intestinal barrier function, and host signaling regulation.^{195,196} Future research should elucidate the roles of SIRT1 in the “microbiota-immune-metabolism” cross-pathways and evaluate its potential therapeutic synergy with microbiota-targeted interventions, including probiotics and dietary fibers.

SIRT1 plays a multi-layered regulatory role in maintaining gut-liver axis function.¹⁹⁷ It strengthens intestinal barrier integrity, regulates microbial metabolic activity, suppresses LPS-TLR4-mediated pro-inflammatory signaling, and coordinates FXR- and TGR5-dependent metabolic-inflammatory pathways, forming a protective network across metabolic, immune, and barrier functions.¹⁹⁸ SIRT1 activation represents a potential strategy to disrupt the pathological feedback loop of “microbiota imbalance-endotoxin entry into the liver-inflammation activation-liver damage,” offering a novel entry point for systemic intervention in MASLD.^{199,200} Future studies should investigate SIRT1’s regulatory roles across varying microbiota compositions, its spatiotemporal dynamics in microbiota-bile acid-immune-circadian rhythm cross-regulation, and its potential as a key target within the “metabolism-inflammation-microbiota” network.²⁰¹

Functional analyses across liver cell types indicate that the role of SIRT1 in MASLD is highly context-dependent rather than uniformly beneficial or harmful. Its effects vary by cell type and disease stage: global SIRT1 knockout mice typically develop exacerbated MASLD phenotypes; hepatocyte-specific SIRT1 deletion primarily aggravates metabolic dysfunction; myeloid-specific knockout exacerbates hepatic inflammation and steatosis in high-fat diet-fed mice;²⁰² while SIRT1 inhibition in HSCs may prove beneficial during fibrosis.²⁰³ Therefore, reviews or intervention strategies discussing SIRT1 in MASLD must avoid the oversimplified assumption that SIRT1 activation is always beneficial and instead adopt a refined, stage- and cell-specific framework.

SIRT1 functions as a key hub integrating metabolic, immune, and stress pathways in MASLD progression.^{80,169,204} It regulates lipid synthesis, fatty acid oxidation, glucose metabolism, and insulin sensitivity *via* deacetylation to maintain hepatocyte energy homeostasis.⁸⁹ In addition, SIRT1 mediates multi-target protection against oxidative stress, coordinates autophagy and ER stress responses, and regulates immune-inflammatory activity.¹⁷⁷ Through enhancement of intestinal barrier function, modulation of microbial composition, and suppression of gut-derived inflammation, SIRT1 establishes a systemic regulatory framework at the gut-liver axis level.

These mechanisms do not act independently but form an integrated regulatory network, with SIRT1 positioned centrally within the “metabolism-immune-organ axis.” In processes including energy sensing, transcriptional control, redox balance, and cell fate determination, SIRT1 consistently occupies a central or upstream role in signal coordination, capable of orchestrating multiple pathways. Thus, targeting SIRT1 holds promise for systemic reprogramming of the complex pathological network in MASLD. The next section will explore advances in the development and translational potential of SIRT1 activators, as illustrated in Figure 2.

Therapeutic potential of SIRT1 activators in MASLD

Previous studies have shown that SIRT1 plays a central regulatory role in multiple pathological processes of MASLD, including lipid metabolism disorders, insulin resistance, immune activation, oxidative stress, and gut-liver barrier dysfunction. SIRT1 exhibits broad multi-pathway regulatory capacity, making interventions targeting SIRT1 a key focus in current MASLD research.¹⁷⁸ Compared with traditional single-target agents, SIRT1 activators simultaneously modulate several critical pathways, including metabolism, immune responses, and oxidative balance, offering a “network reprogramming” therapeutic advantage, particularly in the early stages of the disease when multiple processes are synergistically dysregulated.²⁰⁵ Currently, three major categories of SIRT1-targeted drug candidates are under investigation: natural products, synthetic small-molecule activators, and NAD⁺ precursor supplements. These compounds increase SIRT1 expression or activity, collectively improving hepatic lipid metabolism, insulin signaling, oxidative stress, autophagy, and inflammatory responses, highlighting their strong multi-target pharmacological potential.^{205,206}

Natural product activators

Natural products have attracted attention for SIRT1 activation due to their accessibility, favorable safety profiles, and multi-target properties.^{207,208} Several plant-derived bioactive compounds upregulate SIRT1 expression or enzymatic activity *via* diverse mechanisms, showing positive effects in MASLD-related studies.

Resveratrol: Resveratrol is a natural polyphenol found in grape skins, peanuts, and red wine.²⁰⁹ It was among the earliest identified SIRT1 activators. Resveratrol binds to SIRT1's regulatory domain, increasing its deacetylase activity and modulating downstream signaling pathways such as PGC-1 α , FOXO1, and NF- κ B. This leads to systemic improvements in lipid metabolism, reduced inflammation, and enhanced mitochondrial function.^{210–212} In high-fat diet-induced MASLD models, resveratrol significantly reduces hepatic lipid droplet area, suppresses SREBP-1c and fatty acid synthase expression, and elevates carnitine palmitoyltransferase 1A levels, thereby decreasing lipid accumulation.²¹³ It also downregulates inflammatory cytokines, including TNF- α and IL-6,

through the SIRT1–NF- κ B axis, mitigating chronic inflammation.²¹⁴ Moreover, resveratrol improves gut microbiota composition and intestinal barrier integrity, limiting endotoxin transfer.²¹⁵ Despite these pharmacological benefits, low oral bioavailability remains a major limitation for clinical application.²¹⁶

Curcumin: Curcumin, a yellow polyphenol derived from turmeric, is known for its antioxidant and anti-inflammatory properties.²¹⁷ It increases SIRT1 expression and activates the AMPK–SIRT1–PGC-1 α pathway, inhibiting lipogenesis and promoting mitochondrial β -oxidation.^{218,219} Curcumin also activates the Nrf2–HO-1 pathway, reducing ROS levels and protecting the liver from oxidative stress-induced damage.²²⁰ In animal studies, curcumin decreases MDA levels, enhances catalase and SOD activity, and reduces lipid peroxidation.²²¹ It also inhibits NLRP3 inflammasome activation, lowering IL-1 β and caspase-1 expression and limiting hepatocyte pyroptosis. In a randomized controlled clinical trial, curcumin supplementation significantly reduced body mass index.²²² However, poor solubility and stability restrict its therapeutic application, necessitating the development of nanocarriers or other delivery strategies to improve bioavailability.²²³

Quercetin: Quercetin, a flavonoid present in foods such as onions, apples, and buckwheat,²²⁴ has demonstrated the ability to activate SIRT1, regulating cellular energy homeostasis and metabolism. Quercetin upregulates SIRT1 expression and, *via* the PI3K/Akt and FOXO1 pathways, modulates glucose metabolism and insulin signaling, alleviating insulin resistance.²²⁵ In MASLD animal models, quercetin reduces hepatic triglyceride levels, increases AMPK phosphorylation, and improves insulin sensitivity, as reflected by HOMA-IR index reductions.²²⁶ Quercetin also suppresses NF- κ B-mediated inflammatory responses, reducing pro-inflammatory cytokines (TNF- α , IL-6,²²⁷ induces autophagy to facilitate lipid droplet degradation, improving hepatic adaptation to metabolic stress.²²⁸ Its promising multi-pathway effects make quercetin a widely used dietary supplement,²²⁹ and further structural optimization may enhance specificity and stability for therapeutic development.

Naringin and naringenin: Naringin and naringenin, flavonoids derived from citrus fruits, activate SIRT1 and regulate key metabolic pathways, including AMPK signaling.²³⁰ In high-fat diet-induced MASLD models, naringin improves liver function, reflected by decreased serum ALT and AST levels. Its derivatives modulate the Wnt/ β -catenin pathway and inhibit PDGF-BB-induced HSC activation, suggesting antifibrotic potential.²³¹ Naringenin, the aglycone of naringin, primarily targets ER stress pathways and reduces lipid droplet formation,²³² decreasing hepatocyte apoptosis and preserving liver function. Both compounds are naturally occurring and generally safe, suitable for functional foods, but limited solubility and poor plasma stability restrict pharmaceutical development. Research is ongoing to improve bioavailability and chemical stability for MASLD therapy.²³³

Procyanidins: Procyanidins, polyphenolic compounds abundant in grape seeds, blueberries, and other fruits,²³⁴ are recognized for their antioxidant properties. They activate the SIRT1–AMPK–PGC-1 α pathway, reducing lipid synthesis and promoting fatty acid oxidation.²³⁵ Procyanidins support gut-liver axis function by upregulating tight junction proteins (e.g., zonula occludens-1, claudin-1), limiting endotoxin translocation, and protecting the liver from endotoxemia and inflammation.²³⁶ They also promote hepatocyte autophagy, facilitating the clearance of damaged mitochondria and reducing ROS production, alleviating inflammatory and lipid metabolism disorders.²³⁷ Due to their combined effects on oxidative stress, lipid metabolism, and intestinal barrier in-

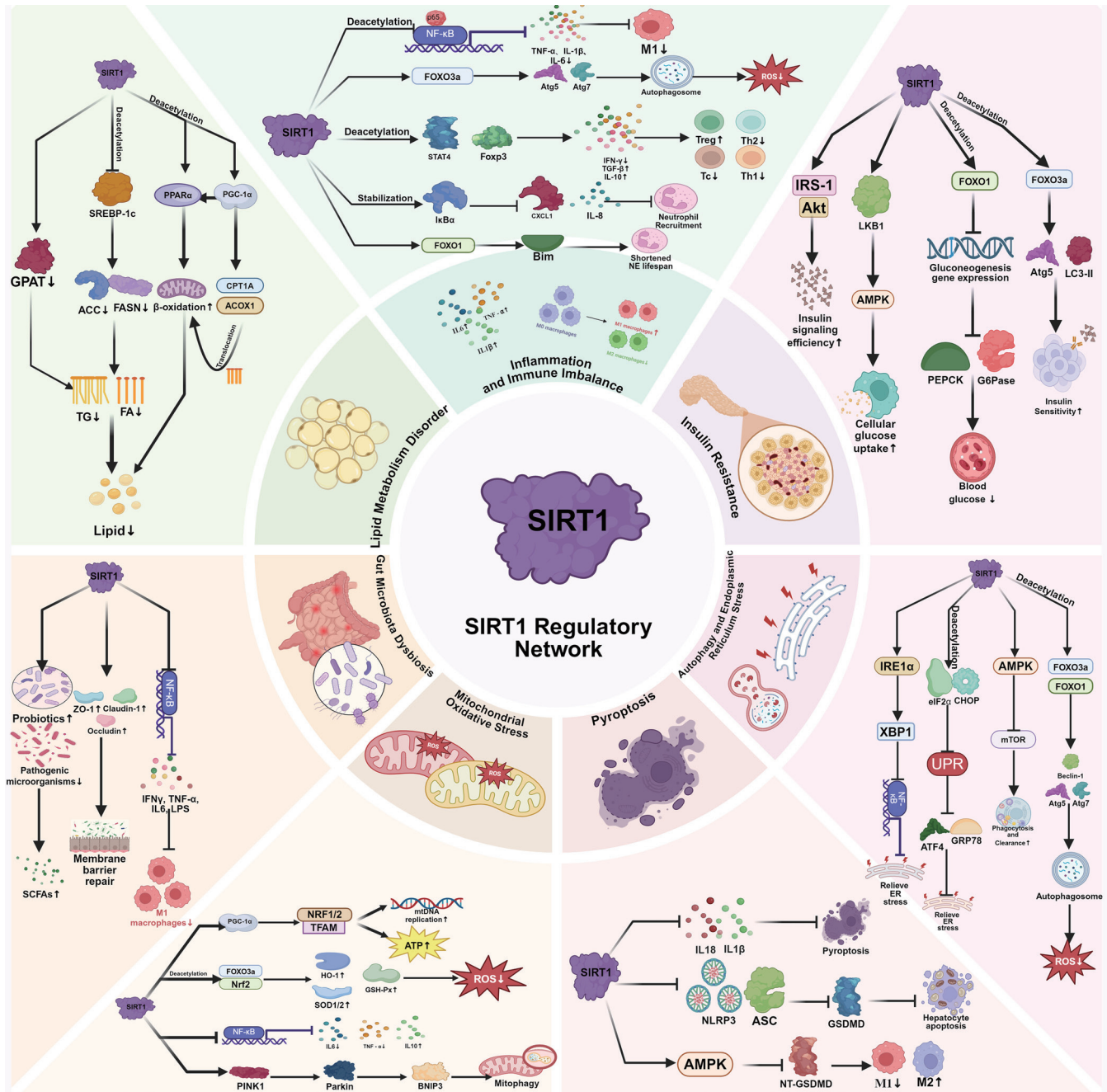


Fig. 2. Mechanistic Roles of SIRT1 in MASLD. Created with BioRender. ACOX1, acyl-coA oxidase 1; ACC, acetyl-coA carboxylase; Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; ASC, apoptosis-associated speck-like protein containing a CARD; Atg5, autophagy-related 5; Atg7, autophagy-related 7; ATP, adenosine triphosphate; BNIP3, BCL2 interacting protein 3; CPT1A, carnitine palmitoyltransferase 1A; CXCL1, C-X-C motif chemokine ligand 1; eIF2 α , eukaryotic translation initiation factor 2 α ; FASN, fatty acid synthase; FOXO3a, forkhead box O3a; Foxp3, forkhead box p3; GPAT, glycerol-3-phosphate acyltransferase; G6Pase, glucose-6-phosphatase; GSH-Px, glutathione peroxidase; HO-1, heme oxygenase-1; IFN γ , interferon gamma; I κ B α , inhibitor of nuclear factor kappa B α ; IRE1 α , inositol-requiring enzyme 1 α ; IRS-1, insulin receptor substrate 1; LKB1, liver kinase B1; mtDNA, mitochondrial DNA; mTOR, mammalian target of rapamycin; NT-GSDMD, N-terminal gasdermin D; Nrf2, nuclear factor erythroid 2-related factor 2; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator 1 α ; PEPCK, phosphoenolpyruvate carboxykinase; PPAR α , peroxisome proliferator-activated receptor α ; PINK1, phosphatase and tensin homolog-induced kinase 1; ROS, reactive oxygen species; SOD1/2, superoxide dismutase 1/2; STAT4, signal transducer and activator of transcription 4; Tc, cytotoxic T cell; TFAM, mitochondrial transcription factor A; TG, triglyceride; Treg, regulatory T cell; Th1, T helper 1 cell; Th2, T helper 2 cell; ↑, up-regulated expression; ↓, down-regulated expression.

tegrity, procyanidins are considered promising candidates for MASLD therapy.

Although natural compounds such as resveratrol, quercetin, and curcumin target multiple pathways and show efficacy

in preclinical MASLD models, their broad activity spectrum may result in off-target interactions.²³⁸ This complicates mechanistic interpretation and may lead to false-positive or irreproducible findings in high-throughput screening.²³⁹

Moreover, pharmacokinetic limitations, including low bioavailability and rapid metabolism, must be carefully addressed when translating *in vitro* results to *in vivo* or clinical settings.

Synthetic small molecule SIRT1 activators

Compared with natural products, synthetic SIRT1 activators offer several advantages, including defined molecular structures, high target selectivity, and stable pharmacokinetic profiles, making them a promising direction for the clinical application of SIRT1-targeted therapies.²⁴⁰ Several synthetic SIRT1 activators have been developed, with some advancing into preclinical or early clinical research.

SRT1720: SRT1720 was the first synthetic SIRT1 activator to enter research. It enhances SIRT1 deacetylase activity by binding to its catalytic domain. In high-fat diet-induced models of obesity and MASLD, SRT1720 upregulates PGC-1 α and PPAR α expression, promoting fatty acid β -oxidation and reducing hepatic triglyceride levels. It also inhibits SREBP-1c activity, limiting lipogenesis.⁴¹ Additionally, SRT1720 activates the AMPK pathway and improves IRS-1/Akt signaling, contributing to enhanced insulin sensitivity.^{241,242} Regarding inflammation, it deacetylates the NF- κ B p65 subunit, inhibits NLRP3 inflammasome activity, and alleviates hepatocyte pyroptosis.²⁴³ While SRT1720 has demonstrated hepatoprotective effects in various metabolic disease models, potential toxicity at higher doses poses challenges for clinical translation.

SRT2104: SRT2104, a second-generation synthetic SIRT1 activator, offers improved selectivity and favorable pharmacokinetics.²⁴⁴ In animal models, it reduces hepatic steatosis, lowers serum ALT and AST levels, and increases mitochondrial respiration and adenosine triphosphate production efficiency.²⁴⁵ Early-phase clinical trials indicate that SRT2104 is well tolerated in healthy individuals and patients with metabolic syndrome, with reductions in serum triglycerides and improvements in the HOMA-IR index over short-term treatment.²⁴⁶ Despite these promising results, liver-targeting specificity remains uncertain, and large-scale clinical validation is lacking.

SRT2379, SRT1460, and other derivative molecules: SRT2379, SRT1460, and other structurally refined SIRT1 activators have shown metabolic benefits in models of diabetes, cardiovascular, and neurodegenerative diseases. However, their effects in MASLD remain underexplored. For instance, SRT2379 was withdrawn after failing to meet efficacy expectations in a Phase I trial, highlighting unresolved issues related to tissue specificity and pathological context dependence.

Despite early progress, synthetic SIRT1 activators have faced significant challenges in large-scale and long-term clinical trials.²³⁹ Phase II studies for type 2 diabetes did not achieve primary endpoints for glycemic control, showing only minor improvements in metabolic parameters.²⁴⁶ Similarly, trials in inflammatory diseases failed to meet efficacy endpoints, suggesting limited benefit in complex human conditions. These outcomes may reflect the inadequacy of targeting SIRT1 alone or the absence of a well-defined therapeutic window.²⁴⁴ Adverse effects have included gastrointestinal symptoms, dose limitations, and electrocardiographic abnormalities, such as prolonged QT intervals. Concerns were also raised regarding long-term systemic activation, which may affect reproductive function, bone turnover, and immune regulation. Systemically administered activators do not preferentially enrich in the liver, requiring high systemic exposure to reach therapeutic concentrations in hepatic tissue, increasing the risk of off-target effects and conflicting responses across liver cell types.^{244,247} These limitations underscore key bottlenecks in

drug development rather than undermining the therapeutic relevance of SIRT1. Future strategies should focus on liver-specific delivery, minimizing systemic exposure, precisely regulating SIRT1 activity, and employing rigorous patient stratification protocols.

NAD⁺ precursor-induced indirect activators

NAD⁺ precursors, such as NMN and NR, act as "indirect SIRT1 activators".²⁴⁸ By increasing intracellular NAD⁺ concentrations, these compounds enhance SIRT1 activity, therefore supporting energy metabolism, reducing oxidative stress, and suppressing inflammation.²⁴⁹ In animal models, NMN and NR reduce hepatic lipid accumulation, improve mitochondrial function, and regulate antioxidant and inflammatory pathways.²⁵⁰ Preliminary human studies, particularly in elderly populations, have reached early-stage clinical investigation, suggesting potential for clinical translation.¹⁸⁴

Overall, natural and synthetic SIRT1 activators rely on SIRT1's multi-dimensional roles in metabolism, inflammation, and oxidative stress regulation in MASLD, as shown in Table 1.^{35,83,87,112,117,120,156,242,251-280} Most activators enhance mitochondrial function and fatty acid β -oxidation via the SIRT1-PGC-1 α axis while inhibiting lipid synthesis mediated by SREBP-1c and ChREBP and positively modulating inflammatory and oxidative pathways such as FOXO1 and NF- κ B. Natural products, with their multi-target regulatory profiles, are more suitable for early-stage metabolic disruption. Synthetic small molecules allow selective targeting but face challenges, including limited efficacy, extrahepatic toxicity, and narrow therapeutic windows. NAD⁺ precursor-based indirect activators complement these strategies by enhancing SIRT1 activity through upstream regulation. Future research should investigate synergistic and selective effects of various activators within multi-target regulatory networks to optimize clinical applicability.

However, therapeutic application of SIRT1 activators is not without risk. SIRT1 activity is highly context-dependent. Overactivation, use during late-stage disease characterized by NAD⁺ depletion, or lack of tissue specificity may result in adverse effects, including oxidative damage, energy imbalance, or cell death.^{29,179,281} Therefore, developing SIRT1-targeted therapies requires careful optimization of dosing, precise control of activity levels, stage-specific intervention timing, tissue- or cell-targeted delivery systems, and integration of NAD⁺ status monitoring to minimize risks and achieve effective outcomes.

Challenges and future perspectives

MASLD is a complex, heterogeneous systemic liver disorder driven by metabolic dysregulation, amplified by inflammation, and sustained by immune imbalance. Its pathogenesis involves multifactorial mechanisms and exhibits significant variability in disease progression among individuals. To date, no specific targeted therapies for MASLD are available. SIRT1, an NAD⁺-dependent deacetylase, regulates multiple critical processes, including lipid metabolism reprogramming, insulin signaling, oxidative stress response, autophagy, and immune balance, forming a regulatory network that spans metabolic, inflammatory, immune, and stress-related pathways.

This review systematically examines the multi-target mechanisms of SIRT1 in MASLD development and progression. It also summarizes recent advances in drug discovery, including natural compounds, synthetic activators, and NAD⁺ precursors, and evaluates their translational potential for MASLD therapy. The findings suggest that activating SIRT1

Table 1. Relevant animal experiments involving SIRT1 agonists

Name	Experimental model	Dosage and administration route	Effects of the drug	References
Resveratrol	129/SvJ mice were fed a high-fat diet for 4 weeks to induce hepatic steatosis	Mice were fed a diet containing 0.4% resveratrol for 4 weeks	Resveratrol induces autophagy via the cAMP-PRKA-AMPK-SIRT1 signaling pathway, promotes fatty acid β -oxidation, reduces intracellular lipid accumulation, and improves hepatic steatosis	251
Resveratrol	Male SD rats were fed a high-yeast and high-fat diet and injected with potassium oxalate (100 mg/kg/day, subcutaneously) to establish a hyperuricemia-related MASLD model	RES was administered by gavage at a dose of 100 mg/kg/d for 12 weeks	Resveratrol activates the SIRT1 pathway to reverse hyperuricemia, improve insulin resistance, inhibit hepatic steatosis, reduce oxidative stress and liver inflammation, and lower insulin resistance	252
Resveratrol	C57BL/6 mice were fed a high-fat diet for 60 days to induce a MASLD model	RSV was added to the feed at a dose of 30 mg/kg/d for 60 days	Resveratrol reduces the liver weight of HFD mice, inhibits the NF- κ B inflammatory pathway by activating the AMPKa-SIRT1 pathway, and reduces liver inflammation	253
Resveratrol	Male C57BL/6J mice were fed a high-fat diet for 4 weeks to induce a MASLD model	RSV was orally administered by gavage at doses of 50 and 100 mg/kg/d for 4 weeks	Resveratrol effectively improves liver steatosis and metabolic disorders, reduces the expression of genes related to lipid and glucose uptake, regulates the gut microbiota, repairs intestinal tight junctions, and alleviates liver inflammation	254
Resveratrol	Male C57BL/6J mice were fed a high-fructose diet for 10 weeks to induce a MASLD model	RSV was administered by gavage at a dose of 25 mg/kg/d for 6 weeks	RSV regulates the gut microbiota to increase the levels of valeric acid and caproic acid in feces, activates the AMPK signaling pathway, and enhances lipid metabolism	255
Resveratrol	Male C57BL/6J mice were intraperitoneally injected with tunicamycin for 2 weeks to induce a mouse model of hepatic steatosis and injury	Resveratrol was orally administered at a dose of 100 mg/kg/d for 2 weeks	Resveratrol effectively alleviates ER stress, improves hepatic steatosis, and inhibits the expression of inflammatory factors	256
Resveratrol	GK rats were fed a high-fat diet containing 10% fat for 4 weeks to induce a MASLD model	A mixture of Cur and Res (at a ratio of 8:2) was administered by gavage at a dose of 150 mg/kg/d for 4 weeks	Cur + Res significantly reduces the blood lipid levels in MASLD rats, improves liver function, and alleviates hepatic steatosis	257
Curcumin	Male C57BL/6J mice were fed a methionine- and choline-deficient diet for 3 weeks to induce hepatic steatosis	Curcumin was orally administered by gavage at a dose of 100 mg/kg/d for 3 weeks	Curcumin reduces liver lipid accumulation in MCD diet-fed mice, alleviates inflammation, activates the expression of antioxidant proteins, and restores the expression of 8 O-GlcNAcylation-modified proteins	258
Curcumin	C57BL/6J mice were fed a high-fat and high-fructose diet for 18 weeks to induce a MASLD model	Curcumin was administered by gavage at doses of 50 and 150 mg/kg/d for 6 weeks	Curcumin directly inhibits function and indirectly regulates the expression of SLC13A5 and ACLY by activating the AMPK-mTOR signaling pathway, thereby restoring citrate homeostasis in the hepatocyte cytoplasm	259
Curcumin	Male C57BL/6 mice were fed a high-fat diet for 13 weeks to induce a MASLD model	Curcumin was administered by gavage at a dose of 100 mg/kg/d for 13 weeks	Curcumin improves insulin sensitivity, lowers insulin levels and the HOMA-IR index, regulates the levels of autophagy-related proteins, alleviates hepatic steatosis, and reduces liver triglyceride levels	260

(continued)

Table 1. (continued)

Name	Experimental model	Dosage and administration route	Effects of the drug	References
Curcumin	Male C57BL/6 mice were fed a high-fat diet and 30% high-fructose water for 8 weeks to induce a MASLD model	Curcumin was administered by gavage at doses of 50 and 100 mg/kg/d for 4 weeks	Curcumin treatment significantly reduces liver lipid accumulation in HFHF-fed mice, lowers serum TG, TC, non-esterified fatty acid, and alanine aminotransferase levels, and reduces liver weight and the liver-to-body weight ratio	261
Quercetin	Male SD rats were fed a high-fat diet for 4 weeks to induce a MASLD model	QUE was administered by gavage at doses of 80, 40, and 20 mg/kg/d for 4 weeks	QUE improves plasma TC and TG concentrations, glucose tolerance, liver fat droplet accumulation, and ballooning degeneration in MASLD rats	262
Quercetin	Male Wistar rats in the high-fat diet group were fed for 6 weeks to induce a MASLD model	Quercetin was added to the diet at a proportion of 0.05 wt% for 3 weeks	Quercetin can regulate the gut microbiota, improve bile acid metabolism, alleviate liver inflammation, and regulate lipid metabolism	263
Quercetin	Male C57BLKS/J mice were fed a high-fat diet for 8 weeks to induce a MASLD model	Quercetin was administered by gavage at doses of 50, 100, and 150 mg/kg/d for 8 weeks	Quercetin improves liver weight, liver function indices, lowers fasting blood glucose and insulin resistance, reduces liver glycogen and free fatty acid accumulation, and restores cholesterol homeostasis by targeting the mTOR/YY1 signaling pathway	264
Quercetin	Male C57BL/6J mice were fed a high-fat diet for 12 weeks to induce a MASLD model	Quercetin was administered by gavage at doses of 50 and 100 mg/kg/d for 12 weeks	Quercetin improves biochemical indices and liver lipid accumulation in HFD mice, alleviates liver lipid peroxidation, and inhibits liver ferroptosis	265
Quercetin	Male C57BL/6 mice were fed a high-fat diet containing 60% fat for 15 weeks to induce a MASLD model	0.5% quercetin was added to the high-fat diet for 15 weeks	Quercetin can regulate the gut microbiota and their metabolites, improve lipid metabolism, intestinal barrier function, and systemic inflammation	266
Quercetin	Male C57BL/6 mice were fed an HFD for 12 weeks to induce insulin resistance and adipose tissue inflammation	0.1% quercetin was added to the high-fat diet for 12 weeks	Quercetin improves HFD-induced obesity and insulin resistance in mice, alleviates adipose tissue inflammation, activates the AMPK α 1/SIRT1 and related anti-inflammatory signaling pathways, and inhibits M1 polarization and inflammation of adipose tissue macrophages	267
Quercetin	Male C57BL/6J mice were fed a MCD diet for 4 weeks to induce a MASLD model	Quercetin was orally administered by gavage at doses of 20 and 80 mg/kg/d for 4 weeks	Quercetin improves MASLD-related cellular homeostatic dysfunction via an AMPK-mediated autophagic pathway	268
Hesperidin	Male C57BL/6J mice were fed an HFD for 16 weeks to induce hepatic steatosis	HES was administered by gavage at doses of 150 and 300 mg/kg/d for 16 weeks	HES promotes fatty acid β -oxidation, activates the SIRT1/PGC1 α pathway, improves insulin sensitivity, and ameliorates liver lipid accumulation and liver injury	269
Hesperidin	Male C57BL/6J mice were fed a high-fat diet for 16 weeks to induce a MASLD model	0.2% (wt/wt) hesperidin was added to the diet for 16 weeks	HES intervention can reduce mouse body weight, liver and fat weights, blood lipid and liver enzyme levels, inhibit liver lipid accumulation, and has no effect on food and energy intake	270

(continued)

Table 1. (continued)

Name	Experimental model	Dosage and administration route	Effects of the drug	References
Hesperidin	Male C57BL/6 mice were fed a high-fat diet for 12 weeks to induce a MASLD model	HDN was administered by gavage at doses of 150 and 300 mg/kg/d for 12 weeks	HDN activates AMPK, down-regulates the expression of SREBP-1C, ACC, and FAS, improves HFD-induced hepatic steatosis and injury in mice, and inhibits lipid accumulation in OA-induced HepG2 cells	271
Neohesperidin	Male C57BL/6 mice were fed a high-fat diet for 12 weeks to induce a MASLD model	NHP was administered by gavage at a dose of 50 mg/kg/d for 12 weeks	NHP promotes PGC-1 α expression by activating AMPK, increases mitochondrial biogenesis, and alleviates HFD-induced hepatic steatosis and insulin resistance in mice	272
Tetrahydro-palmitate	C57BL/6J mice were fed an HFD for 16 weeks to induce a MASLD model	THP was administered by gavage at doses of 40 and 80 mg/kg/day for 8 weeks	THP activates the AMPK-SREBP-1c-Sirt1 axis, promotes fatty acid oxidation, reduces body weight, liver weight, and blood lipid levels in HFD mice, improves hepatic steatosis and liver injury, reduces intracellular lipid accumulation, and protects cells from lipotoxic injury	83
11 β -HSD1	Rats were fed a high-fat diet for 8 weeks and intraperitoneally injected with streptozotocin to induce a MASLD model	H8-L was orally administered at a dose of 3 mg/kg/d, and H8-H and curcumin were administered at a dose of 6 mg/kg/d for 4 weeks	H8 balances lipid metabolism and exerts an anti-inflammatory effect by inhibiting 11 β -HSD1 and up-regulating the AMPK/SIRT1 signaling pathway	112
Isoquercitrin	Male C57BL/6J mice were fed a high-fat diet for 22 weeks to induce a MASH model	IQ was administered by gavage at doses of 50, 100, and 200 mg/kg/d for 20 weeks	IQ can effectively restore liver function in MASH model mice, alleviate inflammation and lipid accumulation, reduce oxidative stress levels, improve mitochondrial function, and enhance liver metabolic function	273
Formononetin	C57BL/6 mice were fed a MCD diet for 6 weeks to induce a MASH mouse model	FMNT was administered by gavage at doses of 25, 50, and 100 mg/kg/d for 6 weeks	FMNT promotes fatty acid β -oxidation, regulates liver lipid metabolism, and alleviates hepatocyte steatosis in MASH mice by activating the SIRT1/PGC-1 α /PPAR α pathway	87
Grape Polyphenols	Male C57BL/6J mice were fed a Western diet for 23 weeks to induce hepatic steatosis	1% GPs were added to the diet for 23 weeks	GPs can change the short-chain fatty acid profile, increase intestinal carbohydrate oxidation, reduce the delivery of liver lipogenesis substrates, and improve WD-induced obesity and hepatic steatosis	274
M. esculenta polysaccharide	Male C57BL/6J mice were fed a high-fat diet for 8 weeks to induce a MASLD model	MCP was administered by gavage at doses of 50–400 mg/kg/d for 8 weeks	MCP activates the AMPK/Sirt1 pathway, increases the expression of p-AMPK and Sirt1, inhibits fatty acid and TG synthesis, and prevents lipotoxicity	275
Naringenin	Male apolipoprotein E-knockout (ApoE $^{-/-}$) mice were used to establish a MASH animal model	NAR was administered by gavage at doses of 100 mg/kg/d and 200 mg/kg/d for 12 weeks	NAR can activate the liver SIRT1-mediated signaling pathway, regulate lipid metabolism, inflammation, oxidative stress, fibrosis, and liver aging	35
Canagliflozin	Male Wistar rats were fed a high-fat and high-fructose diet and drank 25% fructose water for 12 weeks to induce a MASLD model	Canagliflozin was orally administered at a dose of 10 mg/kg/d for 12 weeks	CANA alleviates hepatic steatosis and obesity by activating adipose autophagy and the AMPK signaling pathway	156

(continued)

Table 1. (continued)

Name	Experimental model	Dosage and administration route	Effects of the drug	References
Tristetraprolin	Ttp-knockout mice were used to establish an MASLD model	Metformin was orally administered at a dose of 200 mg/kg/d for 4 weeks	Metformin activates TTP via AMPK-Sirt1, inhibits TNF- α production in KCs, and prevents hepatocyte necroptosis; TTP mediates Rheb destabilization and increases lipid autophagy in primary hepatocytes and the liver	117
Paricalcitol	Male SD rats were fed a choline-deficient high-fat diet for 12 weeks to induce a MASLD model	Paricalcitol was intraperitoneally injected at a dose of 0.08 μ g/kg/d for 8 weeks	Paricalcitol effectively reduces oxidative stress and inflammatory responses in the liver of MASLD rats by enhancing the expression of SIRT1 and SIRT3 and reducing protein acetylation	276
Hydrogen sulfide	Male C57BL/6 mice were fed a high-fat diet for 12 weeks to induce a MASLD model	The H ₂ S donor GYY4137 was intraperitoneally injected at doses of 50 and 100 μ mol/kg/d for 4 weeks	Exogenous H ₂ S inhibits hepatic ER stress and improves MASLD by activating the SIRT1/FoxO1/PCSK9 pathway	277
Xiezhuo Tiaozhi formula	Male C57BL/6J mice were fed a high-fat and high-sugar diet for 16 weeks to induce a MASLD model	Administer the XZTZ formula by gavage at doses of 2.08, 4.16, and 8.32 g/kg/d for 16 weeks	The Xiezhuo Tiaozhi formula (XZTZ) modulates the SIRT1 signaling pathway to suppress macrophage pyroptosis, ameliorates hepatic inflammation and lipid deposition in MASLD mice, and regulates glucose and lipid metabolism	120
Huangqin decoction	Male SD rats were fed an HFD for 16 weeks to induce MASLD	HQD was administered by gavage at doses of 400 and 800 mg/kg/d for 8 weeks	HQD alleviates lipid metabolic disorders and insulin resistance in MASLD by regulating lipogenesis and inflammatory responses and activating the Sirt1/NF- κ B pathway	278
SRT1720	The male rats were fed a high-fat diet for 28 days, followed by intraperitoneal injection of 40 mg/kg streptozotocin to induce T2D, and continued on a high-fat diet for 20 weeks thereafter	SRT1720 was dissolved in 0.5% CMC containing 0.025% Tween 20 and administered daily at a dose of 100 mg/kg, or its vehicle (10 mL/kg) was given by oral gavage for 8 weeks	SRT1720 improved liver histology and reduced inflammation, steatosis, and fibrosis in diabetic rats on a high-fat diet	242
SRT1720	C57BL/6J mice were fed a high-fat diet until the end of their life	a standard AIN-93G diet supplemented with 100mg/kg SRT1720 beginning at 6 months of age for the remainder of their life	SRT1720 extends lifespan and improves health in mice fed a standard diet	279
SRT2104	Either STZ (50 mg/kg/day, dissolved in 0.1 M sodium citrate, pH 4.5; Sigma-Aldrich) or sodium citrate was intraperitoneally injected into the 8-week-old male mice once every day, for 5 consecutive days	SRT2104 was added to the diet at a dose of 1.33g drug per kg of chow, formulated to provide daily doses of 100mg/kg	SRT2104 elevated SIRT1 protein and inactivated P53 under both the diabetic and non-diabetic conditions	280

HFD, high-fat diet; HFHF, high-fat high-fructose diet; HOMA-IR, homeostatic model assessment of insulin resistance; KCs, Kupffer cells; MCD, methionine-choline-deficient diet; p53, tumor protein p53; PCSK9, proprotein convertase subtilisin/kexin type 9; SIRT3, silent information regulator 3; TC, total cholesterol; T2D, type 2 diabetes; YY1, yin yang 1.

could serve as an effective strategy to disrupt the pathological cycle of MASLD, offering advantages in system-wide regulation and synergistic intervention.

However, several challenges remain in translating current SIRT1-targeted strategies from experimental studies to clinical application. First, the complexity and tissue specificity of SIRT1 are not fully understood. Functional variability across liver cell subtypes, immune cells, and metabolic tissues could produce bidirectional or even contradictory effects in different physiological contexts. Second, the optimal dosage and therapeutic window for SIRT1 activation remain unclear; chronic or excessive activation may disrupt metabolic homeostasis or trigger off-target effects. Third, evaluation methods lack standardization. Most studies rely on single-parameter assessments, and a comprehensive model linking SIRT1 activation efficiency with phenotypic improvement is lacking. Finally, selective regulation within the sirtuin family is essential, as overactivation of SIRT1 could disrupt the functional balance of related sirtuins, necessitating careful control of activation intensity and tissue- or subcellular-specific delivery.

To address these limitations, future research should focus on several key directions. Constructing a spatiotemporal-specific functional map of SIRT1 will be essential to understand its dynamic regulatory roles across disease stages, cell subtypes, and tissues. Integration of multi-omics with single-cell approaches can identify key pathways and network hubs influenced by SIRT1, supporting the development of optimized intervention strategies. Designing personalized therapeutic regimens that combine SIRT1 activators with complementary pathways, such as AMPK, Nrf2, or FXR, may enhance precision. Developing cell-type-specific SIRT1 regulators—for example, hepatocyte-targeted molecules using GalNAc ligands or KC-specific nanoparticles—may allow targeted activation, while selective inhibition in cells such as activated HSCs could also be explored. Furthermore, establishing molecular probes and animal models to monitor SIRT1 activity in real time, along with NAD⁺ level assessment, will help guide interventions and minimize adverse effects. Expanding real-world data collection and employing advanced translational models will be important for evaluating the applicability and safety of SIRT1-based interventions across diverse metabolic phenotypes.

Conclusions

SIRT1 represents a mechanistically validated target with notable progress in early-stage drug development for MASLD. With further in-depth analysis of its regulatory network and continued optimization of activator design, SIRT1 holds significant potential as a breakthrough target for multi-pathway, systemic, and precise intervention in MASLD.

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Conflict of interest

The authors have no conflicts of interests related to this publication.

Author contributions

Writing – review & editing, writing – original draft (HZ, DW, QW, YWu, ZG, LW, YWang, QZ, LS, BS, GY, WL), formal analysis (HZ), conceptualization (HZ, GY, WL), supervision, and funding acquisition (GY, WL). All authors have approved the final version and publication of the manuscript.

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