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Review Article

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

Houyan Zhang[1,2#], Dongjie Wu[1#], Qingjuan Wu[1], Yanxuan Wu[2], Ziwei Guo[1], Li Wang[1], Yi Wang[1,3], Qian Zeng[4], Liang Shi[2], Bin Shi[2], Gongchang Yu[2*] and Wenliang Lv[1*]

[1]Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China; [2]Neck-Shoulder and Lumbocrural Pain Hospital of Shandong First Medical University, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, Shandong, China; [3]Beijing University of Chinese Medicine, Beijing, China;; [4]National Center for Nanoscience and Technology, Beijing, China

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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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[#]Contributed to this work equally.

[*]**Correspondence to:** Gongchang Yu, Neck-Shoulder and Lumbocrural Pain Hospital of Shandong First Medical University, Shandong First Medical University & Shandong Academy of Medical Sciences, 18877 Jingshi Road, Lixia District, Jinan, Shandong 250000, China. ORCID: https://orcid.org/0000-0002-2029-0960. Tel/Fax: +86-19861401236, E-mail: yugongchang@sdfmu.edu.cn; Wenliang Lv, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, 5 Beixian Ge, Guang'anmen Inner, Xicheng District, Beijing 100053, China. ORCID: https://orcid.org/0000-0002-6866-4394. Tel/Fax: +86-88002638, E-mail: lvwenliang@sohu.com.

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 barrier[15] 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 tissues[17] 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-1α), Forkhead Box O (FOXO), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) 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, H4K16[31]) and transcriptional regulators such as p53,[32] FOXO1/3a,[33] PGC-1α,[34] LKB1,[35] and NF-κB 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 p53[40] 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 upregulating 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)-1β, 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-1α/peroxisome proliferator-activated receptor alpha (PPARα) 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 PPARα and its coactivator PGC-1α through deacetylation, facilitating mitochondrial β-oxidation.[34,87] PGC-1α 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-1α/PPARα axis, thereby improving hepatic metabolic adaptability.[90–92]

Pharmacological studies indicate that SIRT1 activators, including SRT1720, enhance PGC-1α 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 PPARα 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]

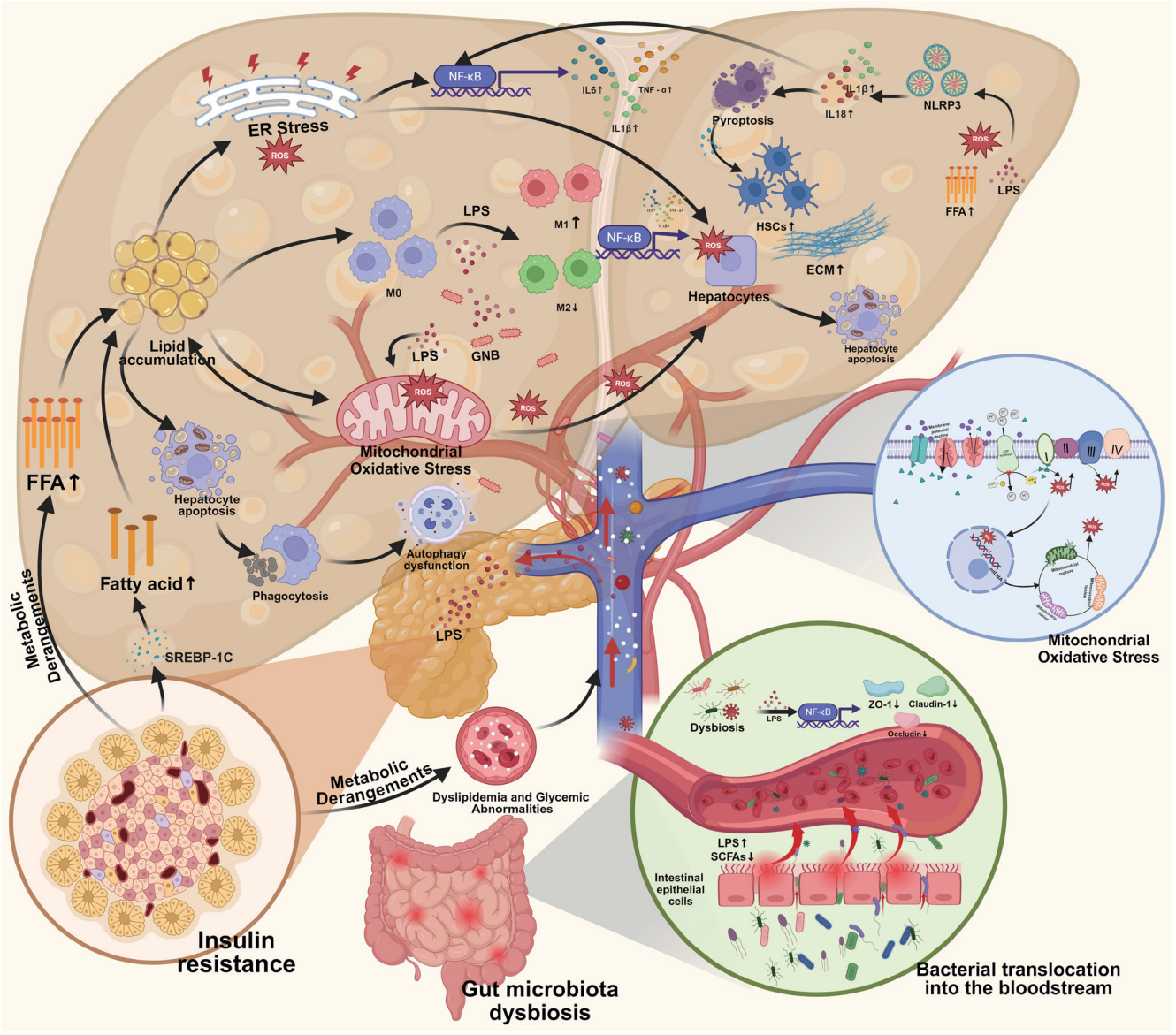

Fig. 1. Multifactorial pathogenesis of MASLD. Created with BioRender. ECM, extracellular matrix; FFA, free fatty acids; GNB, gram-negative bacteria; HSCs, hepatic stellate cells; IL1β, Interleukin-1β; IL18, interleukin-18; IL6, interleukin-6; LPS, lipopolysaccharide; M0, macrophage 0; M1, macrophage 1; M2, macrophage 2; NF-κB, nuclear factor-kappa B; NLRP3, nod-like receptor pyrin domain-containing protein 3; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; SREBP-1c, sterol regulatory element-binding protein 1c; TNF-α, tumor necrosis factor-α; ZO-1, zonula occludens-1; ↑, up-regulated expression; ↓, down-regulated expression.

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-1α, 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 sensitivity and glucose metabolism

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^+-dependent deacetylase, SIRT1 regulates glucose metabolism and insulin sensitivity through multiple signaling axes, alleviating systemic metabolic imbalance.[28]

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-κB p65 subunit, inhibiting its transcriptional activity and reducing the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, 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-κB, 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 IKKβ acetylation, stabilizing IκBα and preventing NF-κB 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-κB 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-1β 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-1β and IL-18, which recruit immune cells and activate NF-κB signaling, amplifying pro-inflammatory mediator production and promoting progression from simple ste-

atosis 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, GSDMD[147]) 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-1β) 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 FOXO1[105] 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 eIF2α 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 IRE1α/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-κB 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-1α, enhancing mitochondrial quantity and function. PGC-1α 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-κB may also produce harmful effects, such as inhibiting p53-mediated antioxidant transcription or sustaining NF-κB 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-κB 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-1α and PPARα. 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-1α, FOXO1, and NF-κB. 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-κB 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-1α 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-1β 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-κB-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-1α 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-

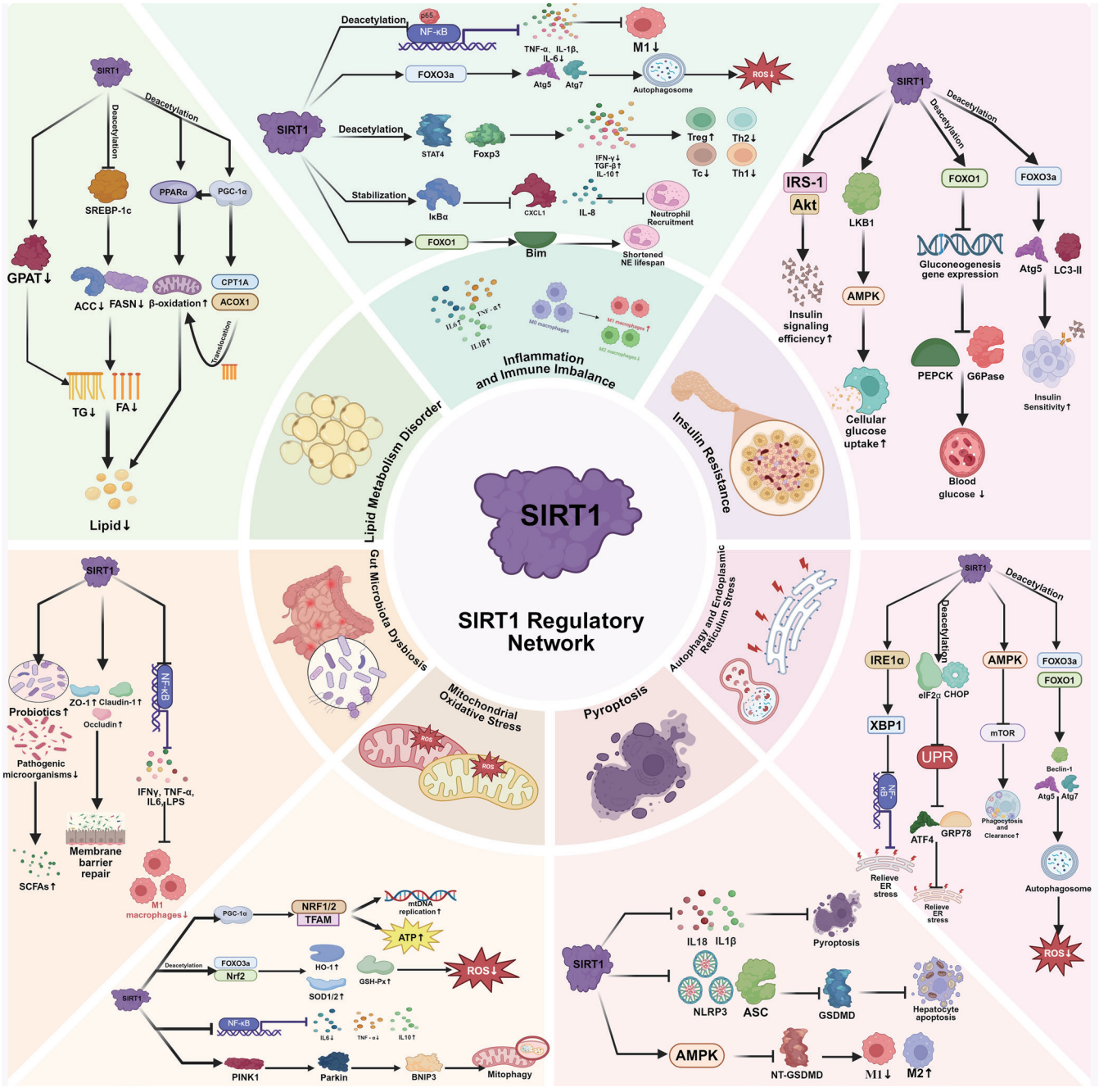

Fig. 2. Mechanistic Roles of SIRT1 in MASLD. Created with BioRender. ACOX1, acyl-coA oxidase 1; ACC, acetyl-coA carboxylase; Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; ASC, apoptosis-associated speck-like protein containing a CARD; Atg5, autophagy-related 5; Atg7, autophagy-related 7; ATP, adenosine triphosphate; BNIP3, BCL2 interacting protein 3; CPT1A, carnitine palmitoyltransferase 1A; CXCL1, C-X-C motif chemokine ligand 1; eIF2α, 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; IFNγ, interferon gamma; IkBα, inhibitor of nuclear factor kappa B α; IRE1α, 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-1α, peroxisome proliferator-activated receptor gamma coactivator 1 α; PEPCK, phosphoenolpyruvate carboxykinase; PPARα, 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-1α and PPARα 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-κB p65 subunit, inhibits its 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-1α axis while inhibiting lipid synthesis mediated by SREBP-1c and ChREBP and positively modulating inflammatory and oxidative pathways such as FOXO1 and NF-κB. 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-κB inflammatory pathway by activating the AMPKα-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 HFHFr-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 AMPKα1/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/PGC1α 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-1α expression by activating AMPK, increases mitochondrial biogenesis, and alleviates HFD-induced hepatic steatosis and insulin resistance in mice	272
Tetrahydropalmatine	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
11β-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 11β-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-1α/PPARα 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 μg/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_2S donor GYY4137 was intraperitoneally injected at doses of 50 and 100 μmol/kg/d for 4 weeks	Exogenous H_2S 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-κB 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	C57BL6/J 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 1.33 g drug per kg of chow, formulated to provide daily doses of 100 mg/kg	SRT2104 elevated SIRT1 protein and inactivated P53 under both the diabetic and non-diabetic conditions	280

HFD, high-fat diet; HFHFr, 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.

References

[1] Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, *et al*. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2022;7(9):851–861. doi:10.1016/S2468-1253(22)00165-0, PMID:35798021.
[2] Hagström H, Shang Y, Hegmar H, Nasr P. Natural history and progression of metabolic dysfunction-associated steatotic liver disease. Lancet Gastroenterol Hepatol 2024;9(10):944–956. doi:10.1016/S2468-1253(24)00193-6, PMID:39243773.
[3] Vitale A, Svegliati-Baroni G, Ortolani A, Cucco M, Dalla Riva GV, Giannini EG, *et al*. Epidemiological trends and trajectories of MAFLD-associated hepatocellular carcinoma 2002-2033: the ITA.LI.CA database. Gut 2023;72(1):141–152. doi:10.1136/gutjnl-2021-324915, PMID:34933916.
[4] Keam SJ. Resmetirom: First Approval. Drugs 2024;84(6):729–735. doi:10.1007/s40265-024-02045-0, PMID:38771485.
[5] Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, *et al*. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med 2024;390(6):497–509. doi:10.1056/NEJMoa2309000, PMID:38324483.
[6] Fan JG, Xu XY, Yang RX, Nan YM, Wei L, Jia JD, *et al*. Guideline for the Prevention and Treatment of Metabolic Dysfunction-associated Fatty Liver Disease (Version 2024). J Clin Transl Hepatol 2024;12(11):955–974. doi:10.14218/JCTH.2024.00311, PMID:39544247.
[7] Paternostro R, Trauner M. Current treatment of non-alcoholic fatty liver disease. J Intern Med 2022;292(2):190–204. doi:10.1111/joim.13531, PMID:35796150.
[8] Cheung A, Figueredo C, Rinella ME. Nonalcoholic Fatty Liver Disease: Identification and Management of High-Risk Patients. Am J Gastroenterol 2019;114(4):579–590. doi:10.14309/ajg.0000000000000058, PMID:30839326.
[9] Polyzos SA, Chrysavgis L, Vachliotis ID, Chartampilas E, Cholongitas E. Nonalcoholic fatty liver disease and hepatocellular carcinoma:Insights in epidemiology, pathogenesis, imaging, prevention and therapy. Semin Cancer Biol 2023;93:20–35. doi:10.1016/j.semcancer.2023.04.010, PMID:37149203.
[10] Sakurai Y, Kubota N, Yamauchi T, Kadowaki T. Role of Insulin Resistance in MAFLD. Int J Mol Sci 2021;22(8):4156. doi:10.3390/ijms22084156, PMID:33923817.
[11] Fromenty B, Roden M. Mitochondrial alterations in fatty liver diseases. J Hepatol 2023;78(2):415–429. doi:10.1016/j.jhep.2022.09.020, PMID:36209983.
[12] Chen Z, Tian R, She Z, Cai J, Li H. Role of oxidative stress in the pathogenesis of nonalcoholic fatty liver disease. Free Radic Biol Med 2020;152:116–141. doi:10.1016/j.freeradbiomed.2020.02.025, PMID:32156524.
[13] Tilg H, Adolph TE, Dudek M, Knolle P. Non-alcoholic fatty liver disease: the interplay between metabolism, microbes and immunity. Nat Metab 2021;3(12):1596–1607. doi:10.1038/s42255-021-00501-9, PMID:34931080.
[14] Ni Y, Lu M, Xu Y, Wang Q, Gu X, Li Y, *et al*. The Role of Gut Microbiota-Bile Acids Axis in the Progression of Non-alcoholic Fatty Liver Disease. Front Microbiol 2022;13:908011. doi:10.3389/fmicb.2022.908011, PMID:35832821.
[15] Martín-Mateos R, Albillos A. The Role of the Gut-Liver Axis in Metabolic Dysfunction-Associated Fatty Liver Disease. Front Immunol 2021;12:660179. doi:10.3389/fimmu.2021.660179, PMID:33936094.
[16] Sauve AA, Wolberger C, Schramm VL, Boeke JD. The biochemistry of sirtuins. Annu Rev Biochem 2006;75:435–465. doi:10.1146/annurev.biochem.74.082803.133500, PMID:16756498.
[17] Chang HC, Guarente L. SIRT1 and other sirtuins in metabolism. Trends Endocrinol Metab 2014;25(3):138–145. doi:10.1016/j.tem.2013.12.001, PMID:24388149.
[18] Feng X, Zhang R, Yang Z, Zhang K, Xing J. Mechanism of Metabolic Dysfunction-associated Steatotic Liver Disease: Important role of lipid metabolism. J Clin Transl Hepatol 2024;12(9):815–826. doi:10.14218/JCTH.2024.00019, PMID:39280069.
[19] Filali-Mouncef Y, Hunter C, Roccio F, Zagkou S, Dupont N, Primard C, *et al*. The ménage à trois of autophagy, lipid droplets and liver disease. Autophagy 2022;18(1):50–72. doi:10.1080/15548627.2021.1895658, PMID:33794741.
[20] Guan G, Chen Y, Dong Y. Unraveling the AMPK-SIRT1-FOXO Pathway: The In-Depth Analysis and Breakthrough Prospects of Oxidative Stress-Induced Diseases. Antioxidants (Basel) 2025;14(1):70. doi:10.3390/an-

tiox14010070, PMID:39857404.
[21] Guo C, Huang Q, Wang Y, Yao Y, Li J, Chen J, *et al*. Therapeutic application of natural products: NAD(+) metabolism as potential target. Phytomedicine 2023;114:154768. doi:10.1016/j.phymed.2023.154768, PMID:36948143.
[22] Zia A, Sahebdel F, Farkhondeh T, Ashrafizadeh M, Zarrabi A, Hushmandi K, *et al*. A review study on the modulation of SIRT1 expression by miRNAs in aging and age-associated diseases. Int J Biol Macromol 2021;188:52–61. doi:10.1016/j.ijbiomac.2021.08.013, PMID:34364937.
[23] Ding RB, Bao J, Deng CX. Emerging roles of SIRT1 in fatty liver diseases. Int J Biol Sci 2017;13(7):852–867. doi:10.7150/ijbs.19370, PMID:28808418.
[24] Ding X, Zhu C, Wang W, Li M, Ma C, Gao B. SIRT1 is a regulator of autophagy: Implications for the progression and treatment of myocardial ischemia-reperfusion. Pharmacol Res 2024;199:106957. doi:10.1016/j.phrs.2023.106957, PMID:37820856.
[25] Liao Z, Cai X, Zheng Y, Lin J, Yang X, Lin W, *et al*. Sirtuin 1 in osteoarthritis: Perspectives on regulating glucose metabolism. Pharmacol Res 2024;202:107141. doi:10.1016/j.phrs.2024.107141, PMID:38490314.
[26] Yang Y, Liu Y, Wang Y, Chao Y, Zhang J, Jia Y, *et al*. Regulation of SIRT1 and Its Roles in Inflammation. Front Immunol 2022;13:831168. doi:10.3389/fimmu.2022.831168, PMID:35359990.
[27] Tozzi R, Cipriani F, Masi D, Basciani S, Watanabe M, Lubrano C, *et al*. Ketone Bodies and SIRT1, Synergic Epigenetic Regulators for Metabolic Health: A Narrative Review. Nutrients 2022;14(15):3145. doi:10.3390/nu14153145, PMID:35956321.
[28] Feng Y, Chen Y, Wu X, Chen J, Zhou Q, Liu B, *et al*. Interplay of energy metabolism and autophagy. Autophagy 2024;20(1):4–14. doi:10.1080/15548627.2023.2247300, PMID:37594406.
[29] Imai S, Guarente L. NAD+ and sirtuins in aging and disease. Trends Cell Biol 2014;24(8):464–471. doi:10.1016/j.tcb.2014.04.002, PMID:24786309.
[30] Xu Y, Wan W. Acetylation in the regulation of autophagy. Autophagy 2023;19(2):379–387. doi:10.1080/15548627.2022.2062112, PMID:35435793.
[31] Hajji N, Wallenborg K, Vlachos P, Füllgrabe J, Hermanson O, Joseph B. Opposing effects of hMOF and SIRT1 on H4K16 acetylation and the sensitivity to the topoisomerase II inhibitor etoposide. Oncogene 2010;29(15):2192–2204. doi:10.1038/onc.2009.505, PMID:20118981.
[32] Xu D, Liu L, Zhao Y, Yang L, Cheng J, Hua R, *et al*. Melatonin protects mouse testes from palmitic acid-induced lipotoxicity by attenuating oxidative stress and DNA damage in a SIRT1-dependent manner. J Pineal Res 2020;69(4):e12690. doi:10.1111/jpi.12690, PMID:32761924.
[33] Song J, Yang M, Xia L, Wang L, Wang K, Xiang Y, *et al*. Aptamer-Conjugated Exosomes Ameliorate Diabetes-Induced Muscle Atrophy by Enhancing SIRT1/FoxO1/3a-Mediated Mitochondrial Function. J Cachexia Sarcopenia Muscle 2025;16(1):e13717. doi:10.1002/jcsm.13717, PMID:39871746.
[34] Taghizadeh M, Maleki MH, Vakili O, Tavakoli R, Zarei P, Dehghanian A, *et al*. Bilirubin, a hepatoprotective agent that activates SIRT1, PGC-1α, and PPAR-α, while inhibiting NF-κB in rats with metabolic-associated fatty liver disease. Sci Rep 2024;14(1):29244. doi:10.1038/s41598-024-80119-5, PMID:39587213.
[35] Hua YQ, Zeng Y, Xu J, Xu XL. Naringenin alleviates nonalcoholic steatohepatitis in middle-aged Apoe(-/-)mice: role of SIRT1. Phytomedicine 2021;81:153412. doi:10.1016/j.phymed.2020.153412, PMID:33234364.
[36] Sun HJ, Xiong SP, Cao X, Cao L, Zhu MY, Wu ZY, *et al*. Polysulfide-mediated sulfhydration of SIRT1 prevents diabetic nephropathy by suppressing phosphorylation and acetylation of p65 NF-κB and STAT3. Redox Biol 2021;38:101813. doi:10.1016/j.redox.2020.101813, PMID:33279869.
[37] Wahab F, Rodriguez Polo I, Behr R. SIRT1 Expression and Regulation in the Primate Testis. Int J Mol Sci 2021;22(6):3207. doi:10.3390/ijms22063207, PMID:33809872.
[38] Fan W, Li X. The SIRT1-c-Myc axis in regulation of stem cells. Front Cell Dev Biol 2023;11:1236968. doi:10.3389/fcell.2023.1236968, PMID:37554307.
[39] Chen D, Pacal M, Wenzel P, Knoepfler PS, Leone G, Bremner R. Division and apoptosis of E2f-deficient retinal progenitors. Nature 2009;462(7275):925–929. doi:10.1038/nature08544, PMID:20016601.
[40] Zhu L, Lu Z, Zhao H. Antitumor mechanisms when pRb and p53 are genetically inactivated. Oncogene 2015;34(35):4547–4557. doi:10.1038/onc.2014.399, PMID:25486431.
[41] Shen S, Shen M, Kuang L, Yang K, Wu S, Liu X, *et al*. SIRT1/SREBPs-mediated regulation of lipid metabolism. Pharmacol Res 2024;199:107037. doi:10.1016/j.phrs.2023.107037, PMID:38070792.
[42] Papageorgiou AA, Litsaki M, Mourmoura E, Papathanasiou I, Tsezou A. DNA methylation regulates Sirtuin 1 expression in osteoarthritic chondrocytes. Adv Med Sci 2023;68(1):101–110. doi:10.1016/j.advms.2023.02.002, PMID:36913826.
[43] Deng XJ, Zheng HL, Ke XQ, Deng M, Ma ZZ, Zhu Y, *et al*. Hsa-miR-34a-5p reverses multidrug resistance in gastric cancer cells by targeting the 3′-UTR of SIRT1 and inhibiting its expression. Cell Signal 2021;84:110016. doi:10.1016/j.cellsig.2021.110016, PMID:33894312.
[44] Han S, Lin F, Ruan Y, Zhao S, Yuan R, Ning J, *et al*. miR-132-3p promotes the cisplatin-induced apoptosis and inflammatory response of renal tubular epithelial cells by targeting SIRT1 via the NF-κB pathway. Int Immunopharmacol 2021;99:108022. doi:10.1016/j.intimp.2021.108022, PMID:34339961.
[45] Menghini R, Casagrande V, Cardellini M, Martelli E, Terrinoni A, Amati F, *et al*. MicroRNA 217 modulates endothelial cell senescence via silent information regulator 1. Circulation 2009;120(15):1524–1532. doi:10.1161/CIRCULATIONAHA.109.864629, PMID:19786632.
[46] Wan Y, Slevin E, Koyama S, Huang CK, Shetty AK, Li X, *et al*. miR-34a regulates macrophage-associated inflammation and angiogenesis in alcohol-induced liver injury. Hepatol Commun 2023;7(4):e0089. doi:10.1097/HC9.0000000000000089, PMID:37026704.
[47] Yoshino J, Mills KF, Yoon MJ, Imai S. Nicotinamide mononucleotide, a key NAD(+) intermediate, treats the pathophysiology of diet- and age-induced diabetes in mice. Cell Metab 2011;14(4):528–536. doi:10.1016/j.cmet.2011.08.014, PMID:21982712.
[48] Cantó C, Gerhart-Hines Z, Feige JN, Lagouge M, Noriega L, Milne JC, *et al*. AMPK regulates energy expenditure by modulating NAD+ metabolism and SIRT1 activity. Nature 2009;458(7241):1056–1060. doi:10.1038/nature07813, PMID:19262508.
[49] da Fonseca ACP, Assis ISDS, Salum KCR, Palhinha L, Abreu GM, Zembrzuski VM, *et al*. Genetic variants in DBC1, SIRT1, UCP2 and ADRB2 as potential biomarkers for severe obesity and metabolic complications. Front Genet 2024;15:1363417. doi:10.3389/fgene.2024.1363417, PMID:38841722.
[50] Li X, Song D, Chen Y, Huang C, Liu A, Wu Q, *et al*. NSD2 methylates AROS to promote SIRT1 activation and regulates fatty acid metabolism-mediated cancer radiotherapy. Cell Rep 2023;42(10):113126. doi:10.1016/j.celrep.2023.113126, PMID:37756162.
[51] Chen DD, Shi Q, Liu X, Liang DL, Wu YZ, Fan Q, *et al*. Aberrant SENP1-SUMO-Sirt3 Signaling Causes the Disturbances of Mitochondrial Deacetylation and Oxidative Phosphorylation in Prion-Infected Animal and Cell Models. ACS Chem Neurosci 2023;14(9):1610–1621. doi:10.1021/acschemneuro.2c00786, PMID:37092685.
[52] Pande S, Raisuddin S. Molecular and cellular regulatory roles of sirtuin protein. Crit Rev Food Sci Nutr 2023;63(29):9895–9913. doi:10.1080/10408398.2022.2070722, PMID:35510883.
[53] Cao Y, Jiang X, Ma H, Wang Y, Xue P, Liu Y. SIRT1 and insulin resistance. J Diabetes Complications 2016;30(1):178–183. doi:10.1016/j.jdiacomp.2015.08.022, PMID:26422395.
[54] Li X. SIRT1 and energy metabolism. Acta Biochim Biophys Sin (Shanghai) 2013;45(1):51–60. doi:10.1093/abbs/gms108, PMID:23257294.
[55] Gofton C, Upendran Y, Zheng MH, George J. MAFLD: How is it different from NAFLD? Clin Mol Hepatol 2023;29(Suppl):S17–S31. doi:10.3350/cmh.2022.0367, PMID:36443926.
[56] De Cól JP, de Lima EP, Pompeu FM, Cressoni Araújo A, de Alvares Goulart R, Bechara MD, *et al*. Underlying Mechanisms behind the Brain-Gut-Liver Axis and Metabolic-Associated Fatty Liver Disease (MAFLD): An Update. Int J Mol Sci 2024;25(7):3694. doi:10.3390/ijms25073694, PMID:38612504.
[57] Drożdż K, Nabrdalik K, Hajzler W, Kwiendacz H, Gumprecht J, Lip GYH. Metabolic-Associated Fatty Liver Disease (MAFLD), Diabetes, and Cardiovascular Disease: Associations with Fructose Metabolism and Gut Microbiota. Nutrients 2021;14(1):103. doi:10.3390/nu14010103, PMID:35010976.
[58] Hu Z, Yue H, Jiang N, Qiao L. Diet, oxidative stress and MAFLD: a mini review. Front Nutr 2025;12:1539578. doi:10.3389/fnut.2025.1539578, PMID:40104813.
[59] Yan Y, Zhang W, Wang Y, Yi C, Yu B, Pang X, *et al*. Crosstalk between intestinal flora and human iron metabolism: the role in metabolic syndrome-related comorbidities and its potential clinical application. Microbiol Res 2024;282:127667. doi:10.1016/j.micres.2024.127667, PMID:38442456.
[60] Griffin JD, Buxton JM, Culver JA, Barnes R, Jordan EA, White AR, *et al*. Hepatic Activin E mediates liver-adipose inter-organ communication, suppressing adipose lipolysis in response to elevated serum fatty acids. Mol Metab 2023;78:101830. doi:10.1016/j.molmet.2023.101830, PMID:38787338.
[61] Saponaro C, Sabatini S, Gaggini M, Carli F, Rosso C, Positano V, *et al*. Adipose tissue dysfunction and visceral fat are associated with hepatic insulin resistance and severity of NASH even in lean individuals. Liver Int 2022;42(11):2418–2427. doi:10.1111/liv.15377, PMID:35900229.
[62] Badmus OO, Hillhouse SA, Anderson CD, Hinds TD, Stec DE. Molecular mechanisms of metabolic associated fatty liver disease (MAFLD): functional analysis of lipid metabolism pathways. Clin Sci (Lond) 2022;136(18):1347–1366. doi:10.1042/CS20220572, PMID:36148775.
[63] Bansal SK, Bansal MB. Pathogenesis of MASLD and MASH - role of insulin resistance and lipotoxicity. Aliment Pharmacol Ther 2024;59(Suppl 1):S10–S22. doi:10.1111/apt.17930, PMID:38451123.
[64] Mansouri A, Gattolliat CH, Asselah T. Mitochondrial Dysfunction and Signaling in Chronic Liver Diseases. Gastroenterology 2018;155(3):629–647. doi:10.1053/j.gastro.2018.06.083, PMID:30012333.
[65] Huby T, Gautier EL. Immune cell-mediated features of non-alcoholic steatohepatitis. Nat Rev Immunol 2022;22(7):429–443. doi:10.1038/s41577-021-00639-3, PMID:34741169.
[66] Fu J, Wu H. Structural Mechanisms of NLRP3 Inflammasome Assembly and Activation. Annu Rev Immunol 2023;41:301–316. doi:10.1146/annurev-immunol-081022-021207, PMID:36750315.
[67] Feng Y, Li W, Wang Z, Zhang R, Li Y, Zang L, *et al*. The p-STAT3/ANXA2 axis promotes caspase-1-mediated hepatocyte pyroptosis in non-alcoholic steatohepatitis. J Transl Med 2022;20(1):497. doi:10.1186/s12967-022-03692-1, PMID:36324154.
[68] Brenner C, Galluzzi L, Kepp O, Kroemer G. Decoding cell death signals in liver inflammation. J Hepatol 2013;59(3):583–594. doi:10.1016/j.jhep.2013.03.033, PMID:23567086.
[69] Fang J, Yu CH, Li XJ, Yao JM, Fang ZY, Yoon SH, *et al*. Gut dysbiosis in nonalcoholic fatty liver disease: pathogenesis, diagnosis, and therapeutic implications. Front Cell Infect Microbiol 2022;12:997018. doi:10.3389/fcimb.2022.997018, PMID:36425787.
[70] Ghosh S, Whitley CS, Haribabu B, Jala VR. Regulation of Intestinal Barrier Function by Microbial Metabolites. Cell Mol Gastroenterol Hepatol 2021;11(5):1463–1482. doi:10.1016/j.jcmgh.2021.02.007, PMID:33610769.
[71] Shi L, Jin L, Huang W. Bile Acids, Intestinal Barrier Dysfunction, and Related Diseases. Cells 2023;12(14):1888. doi:10.3390/cells12141888, PMID:37508557.

[72] Park BS, Lee JO. Recognition of lipopolysaccharide pattern by TLR4 complexes. Exp Mol Med 2013;45(12):e66. doi:10.1038/emm.2013.97, PMID:24310172.
[73] Jia W, Xie G, Jia W. Bile acid-microbiota crosstalk in gastrointestinal inflammation and carcinogenesis. Nat Rev Gastroenterol Hepatol 2018;15(2):111–128. doi:10.1038/nrgastro.2017.119, PMID:29018272.
[74] Thibaut MM, Bindels LB. Crosstalk between bile acid-activated receptors and microbiome in entero-hepatic inflammation. Trends Mol Med 2022;28(3):223–236. doi:10.1016/j.molmed.2021.12.006, PMID:35074252.
[75] Li Y, Wong K, Giles A, Jiang J, Lee JW, Adams AC, *et al*. Hepatic SIRT1 attenuates hepatic steatosis and controls energy balance in mice by inducing fibroblast growth factor 21. Gastroenterology 2014;146(2):539–49.e7. doi:10.1053/j.gastro.2013.10.059, PMID:24184811.
[76] Zhao H, Tian Y, Zuo Y, Zhang X, Gao Y, Wang P, *et al*. Nicotinamide riboside ameliorates high-fructose-induced lipid metabolism disorder in mice via improving FGF21 resistance in the liver and white adipose tissue. Food Funct 2022;13(23):12400–12411. doi:10.1039/d2fo01934e, PMID:36373585.
[77] Ben-Moshe S, Itzkovitz S. Spatial heterogeneity in the mammalian liver. Nat Rev Gastroenterol Hepatol 2019;16(7):395–410. doi:10.1038/s41575-019-0134-x, PMID:30936469.
[78] Wang J, Bao S, An Q, Li C, Feng J. Roles of extracellular vesicles from different origins in metabolic-associated fatty liver disease: progress and perspectives. Front Immunol 2025;16:1544012. doi:10.3389/fimmu.2025.1544012, PMID:40129979.
[79] Stanger BZ. Probing hepatocyte heterogeneity. Cell Res 2015;25(11):1181–1182. doi:10.1038/cr.2015.117, PMID:26403190.
[80] Nguyen LT, Chen H, Zaky A, Pollock C, Saad S. SIRT1 overexpression attenuates offspring metabolic and liver disorders as a result of maternal high-fat feeding. J Physiol 2019;597(2):467–480. doi:10.1113/JP276957, PMID:30381838.
[81] Kamchonemenukool S, Koh YC, Ho PY, Pan MH, Weerawatanakorn M. Fatty Acid Esterification of Octacosanol Attenuates Triglyceride and Cholesterol Synthesis in Mice. J Agric Food Chem 2025;73(4):2430–2442. doi:10.1021/acs.jafc.4c10201, PMID:39808738.
[82] Chyau CC, Wang HF, Zhang WJ, Chen CC, Huang SH, Chang CC, *et al*. Antrodan Alleviates High-Fat and High-Fructose Diet-Induced Fatty Liver Disease in C57BL/6 Mice Model via AMPK/Sirt1/SREBP-1c/PPARγ Pathway. Int J Mol Sci 2020;21(1):360. doi:10.3390/ijms21010360, PMID:31935815.
[83] Yin X, Liu Z, Wang J. Tetrahydropalmatine ameliorates hepatic steatosis in nonalcoholic fatty liver disease by switching lipid metabolism via AMPK-SREBP-1c-Sirt1 signaling axis. Phytomedicine 2023;119:155005. doi:10.1016/j.phymed.2023.155005, PMID:37562090.
[84] Wang S, Moustaid-Moussa N, Chen L, Mo H, Shastri A, Su R, *et al*. Novel insights of dietary polyphenols and obesity. J Nutr Biochem 2014;25(1):1–18. doi:10.1016/j.jnutbio.2013.09.001, PMID:24314860.
[85] Wang RH, Li C, Deng CX. Liver steatosis and increased ChREBP expression in mice carrying a liver specific SIRT1 null mutation under a normal feeding condition. Int J Biol Sci 2010;6(7):682–690. doi:10.7150/ijbs.6.682, PMID:21103071.
[86] Xu F, Gao Z, Zhang J, Rivera CA, Yin J, Weng J, *et al*. Lack of SIRT1 (Mammalian Sirtuin 1) activity leads to liver steatosis in the SIRT1+/- mice: a role of lipid mobilization and inflammation. Endocrinology 2010;151(6):2504–2514. doi:10.1210/en.2009-1013, PMID:20339025.
[87] Liao J, Xie X, Wang N, Wang Y, Zhao J, Chen F, *et al*. Formononetin promotes fatty acid β-oxidation to treat non-alcoholic steatohepatitis through SIRT1/PGC-1α/PPARα pathway. Phytomedicine 2024;124:155285. doi:10.1016/j.phymed.2023.155285, PMID:38185065.
[88] Li Y, Li X, Liu J, Jayavanth P, Bai W, Jiao R. Vitisin A Outperforms Cyanidin-3-O-Glucoside in Triglyceride Reduction by Modulating Hepatic Lipogenesis and Fatty Acid β-Oxidation. Int J Mol Sci 2025;26(4):1521. doi:10.3390/ijms26041521, PMID:40003987.
[89] Yang JW, Zou Y, Chen J, Cui C, Song J, Yang MM, *et al*. Didymin alleviates metabolic dysfunction-associated fatty liver disease (MAFLD) via the stimulation of Sirt1-mediated lipophagy and mitochondrial biogenesis. J Transl Med 2023;21(1):921. doi:10.1186/s12967-023-04790-4, PMID:38115075.
[90] Seok S, Kim YC, Byun S, Choi S, Xiao Z, Iwamori N, *et al*. Fasting-induced JMJD3 histone demethylase epigenetically activates mitochondrial fatty acid β-oxidation. J Clin Invest 2018;128(7):3144–3159. doi:10.1172/JCI97736, PMID:29911994.
[91] Levine DC, Kuo HY, Hong HK, Cedernaes J, Hepler C, Wright AG, *et al*. NADH inhibition of SIRT1 links energy state to transcription during time-restricted feeding. Nat Metab 2021;3(12):1621–1632. doi:10.1038/s42255-021-00498-1, PMID:34903884.
[92] Khan SA, Sathyanarayan A, Mashek MT, Ong KT, Wollaston-Hayden EE, Mashek DG. ATGL-catalyzed lipolysis regulates SIRT1 to control PGC-1α/PPAR-α signaling. Diabetes 2015;64(2):418–426. doi:10.2337/db14-0325, PMID:25614670.
[93] Feige JN, Lagouge M, Canto C, Strehle A, Houten SM, Milne JC, *et al*. Specific SIRT1 activation mimics low energy levels and protects against diet-induced metabolic disorders by enhancing fat oxidation. Cell Metab 2008;8(5):347–358. doi:10.1016/j.cmet.2008.08.017, PMID:19046567.
[94] Kim TH, Yang YM, Han CY, Koo JH, Oh H, Kim SS, *et al*. Gα12 ablation exacerbates liver steatosis and obesity by suppressing USP22/SIRT1-regulated mitochondrial respiration. J Clin Invest 2018;128(12):5587–5602. doi:10.1172/JCI97831, PMID:30300140.
[95] Wu Y, Jiang Y, Guo JQ, Yang ZW, Carvalho A, Qian LL, *et al*. Visceral adipose tissue-directed human kallistatin gene therapy improves adipose tissue remodeling and metabolic health in obese mice. Cell Signal 2023;106:110637. doi:10.1016/j.cellsig.2023.110637, PMID:36813150.
[96] Ren Q, Sun Q, Fu J. Dysfunction of autophagy in high-fat diet-induced non-alcoholic fatty liver disease. Autophagy 2024;20(2):221–241. doi:10.1080/15548627.2023.2254191, PMID:37700498.
[97] Escalona-Garrido C, Vázquez P, Mera P, Zagmutt S, García-Casarrubios E, Montero-Pedrazuela A, *et al*. Moderate SIRT1 overexpression protects against brown adipose tissue inflammation. Mol Metab 2020;42:101097. doi:10.1016/j.molmet.2020.101097, PMID:33049408.
[98] Noriega LG, Feige JN, Canto C, Yamamoto H, Yu J, Herman MA, *et al*. CREB and ChREBP oppositely regulate SIRT1 expression in response to energy availability. EMBO Rep 2011;12(10):1069–1076. doi:10.1038/embor.2011.151, PMID:21836635.
[99] Hu Y, Hai J, Ti Y, Kong B, Yao G, Zhao Y, *et al*. Adipose ZFP36 protects against diet-induced obesity and insulin resistance. Metabolism 2025;164:156131. doi:10.1016/j.metabol.2024.156131, PMID:39761791.
[100] Levine DC, Hong H, Weidemann BJ, Ramsey KM, Affinati AH, Schmidt MS, *et al*. NAD(+) Controls Circadian Reprogramming through PER2 Nuclear Translocation to Counter Aging. Mol Cell 2020;78(5):835–849.e7. doi:10.1016/j.molcel.2020.04.010, PMID:32369735.
[101] Aggarwal S, Trehanpati N, Nagarajan P, Ramakrishna G. The Clock-NAD(+) -Sirtuin connection in nonalcoholic fatty liver disease. J Cell Physiol 2022;237(8):3164–3180. doi:10.1002/jcp.30772, PMID:35616339.
[102] Sathyanarayan A, Mashek MT, Mashek DG. ATGL Promotes Autophagy/Lipophagy via SIRT1 to Control Hepatic Lipid Droplet Catabolism. Cell Rep 2017;19(1):1–9. doi:10.1016/j.celrep.2017.03.026, PMID:28380348.
[103] Zhou S, Tang X, Chen HZ. Sirtuins and Insulin Resistance. Front Endocrinol (Lausanne) 2018;9:748. doi:10.3389/fendo.2018.00748, PMID:30574122.
[104] Long JK, Dai W, Zheng YW, Zhao SP. miR-122 promotes hepatic lipogenesis via inhibiting the LKB1/AMPK pathway by targeting Sirt1 in non-alcoholic fatty liver disease. Mol Med 2019;25(1):26. doi:10.1186/s10020-019-0085-2, PMID:31195981.
[105] Ren H, Shao Y, Wu C, Ma X, Lv C, Wang Q. Metformin alleviates oxidative stress and enhances autophagy in diabetic kidney disease via AMPK/SIRT1-FoxO1 pathway. Mol Cell Endocrinol 2020;500:110628. doi:10.1016/j.mce.2019.110628, PMID:31647955.
[106] Wang RH, Kim HS, Xiao C, Xu X, Gavrilova O, Deng CX. Hepatic Sirt1 deficiency in mice impairs mTorc2/Akt signaling and results in hyperglycemia, oxidative damage, and insulin resistance. J Clin Invest 2011;121(11):4477–4490. doi:10.1172/JCI46243, PMID:21965330.
[107] Zhou B, Zhang Y, Zhang F, Xia Y, Liu J, Huang R, *et al*. CLOCK/BMAL1 regulates circadian change of mouse hepatic insulin sensitivity by SIRT1. Hepatology 2014;59(6):2196–2206. doi:10.1002/hep.26992, PMID:24442997.
[108] Hui X, Zhang M, Gu P, Li K, Gao Y, Wu D, *et al*. Adipocyte SIRT1 controls systemic insulin sensitivity by modulating macrophages in adipose tissue. EMBO Rep 2017;18(4):645–657. doi:10.15252/embr.201643184, PMID:28270525.
[109] Zhang CY, Tan XH, Yang HH, Jin L, Hong JR, Zhou Y, *et al*. COX-2/sEH Dual Inhibitor Alleviates Hepatocyte Senescence in NAFLD Mice by Restoring Autophagy through Sirt1/PI3K/AKT/mTOR. Int J Mol Sci 2022;23(15):8267. doi:10.3390/ijms23158267, PMID:35897843.
[110] Her JY, Lee Y, Kim SJ, Heo G, Choo J, Kim Y, *et al*. Blockage of protease-activated receptor 2 exacerbates inflammation in high-fat environment partly through autophagy inhibition. Am J Physiol Gastrointest Liver Physiol 2021;320(1):G30–G42. doi:10.1152/ajpgi.00203.2020, PMID:33146548.
[111] Zhao X, Yin F, Fu L, Ma Y, Ye L, Huang Y, *et al*. Garlic-derived exosome-like nanovesicles as a hepatoprotective agent alleviating acute liver failure by inhibiting CCR2/CCR5 signaling and inflammation. Biomater Adv 2023;154:213592. doi:10.1016/j.bioadv.2023.213592, PMID:37717364.
[112] Chen Y, Li J, Zhang M, Yang W, Qin W, Zheng Q, *et al*. 11β-HSD1 Inhibitor Alleviates Non-Alcoholic Fatty Liver Disease by Activating the AMPK/SIRT1 Signaling Pathway. Nutrients 2022;14(11):2358. doi:10.3390/nu14112358, PMID:35684158.
[113] Sun X, Cao Z, Ma Y, Shao Y, Zhang J, Yuan G, *et al*. Resveratrol attenuates dapagliflozin-induced renal gluconeogenesis via activating the PI3K/Akt pathway and suppressing the FoxO1 pathway in type 2 diabetes. Food Funct 2021;12(3):1207–1218. doi:10.1039/d0fo02387f, PMID:33432947.
[114] Radak Z, Suzuki K, Posa A, Petrovszky Z, Koltai E, Boldogh I. The systemic role of SIRT1 in exercise mediated adaptation. Redox Biol 2020;35:101467. doi:10.1016/j.redox.2020.101467, PMID:32086007.
[115] Peiseler M, Schwabe R, Hampe J, Kubes P, Heikenwälder M, Tacke F. Immune mechanisms linking metabolic injury to inflammation and fibrosis in fatty liver disease - novel insights into cellular communication circuits. J Hepatol 2022;77(4):1136–1160. doi:10.1016/j.jhep.2022.06.012, PMID:35750137.
[116] Mladenić K, Lenartić M, Marinović S, Polić B, Wensveen FM. The "Domino effect" in MASLD: The inflammatory cascade of steatohepatitis. Eur J Immunol 2024;54(4):e2149641. doi:10.1002/eji.202149641, PMID:38314819.
[117] Park J, Rah SY, An HS, Lee JY, Roh GS, Ryter SW, *et al*. Metformin-induced TTP mediates communication between Kupffer cells and hepatocytes to alleviate hepatic steatosis by regulating lipophagy and necroptosis. Metabolism 2023;141:155516. doi:10.1016/j.metabol.2023.155516, PMID:36773805.
[118] Velikova T, Gulinac M. Novel insights into autophagy in gastrointestinal pathologies, mechanisms in metabolic dysfunction-associated fatty liver disease and acute liver failure. World J Gastroenterol 2024;30(27):3273–3277. doi:10.3748/wjg.v30.i27.3273, PMID:39086749.
[119] Yin Y, Xie Y, Wu Z, Qian Q, Yang H, Li S, *et al*. Preventive Effects of Apple Polyphenol Extract on High-Fat-Diet-Induced Hepatic Steatosis Are Related to the Regulation of Hepatic Lipid Metabolism, Autophagy, and Gut Microbiota in Aged Mice. J Agric Food Chem 2023;71(50):20011–20033.

doi:10.1021/acs.jafc.3c00596, PMID:38055797.
[120] Tian L, Chen J, Yang M, Chen L, Qiu J, Jiang Y, *et al*. Xiezhuo Tiaozhi formula inhibits macrophage pyroptosis in the non-alcoholic fatty liver disease by targeting the SIRT1 pathway. Phytomedicine 2024;131:155776. doi:10.1016/j.phymed.2024.155776, PMID:38851104.
[121] Nakamura K, Zhang M, Kageyama S, Ke B, Fujii T, Sosa RA, *et al*. Macrophage heme oxygenase-1-SIRT1-p53 axis regulates sterile inflammation in liver ischemia-reperfusion injury. J Hepatol 2017;67(6):1232–1242. doi:10.1016/j.jhep.2017.08.010, PMID:28842295.
[122] Savage TM, Fortson KT, de Los Santos-Alexis K, Oliveras-Alsina A, Rouanne M, Rae SS, *et al*. Amphiregulin from regulatory T cells promotes liver fibrosis and insulin resistance in non-alcoholic steatohepatitis. Immunity 2024;57(2):303–318.e6. doi:10.1016/j.immuni.2024.01.009, PMID:38309273.
[123] Wang Y, Yang H, Jia A, Wang Y, Yang Q, Dong Y, *et al*. Dendritic cell Piezo1 directs the differentiation of T(H)1 and T(reg) cells in cancer. Elife 2022;11:e79957. doi:10.7554/eLife.79957, PMID:35993548.
[124] Mammana C, Cox ID, Azzarelli S, Galassi AR, Foti R, Gulizia G, *et al*. Diagnostic value of exercise electrocardiography for predicting a positive scintigraphic test in patients with complete right bundle branch block. Cardiologia 1999;44(8):727–734. PMID:10476598.
[125] Hu T, Fan X, Ma L, Liu J, Chang Y, Yang P, *et al*. TIM4-TIM1 interaction modulates Th2 pattern inflammation through enhancing SIRT1 expression. Int J Mol Med 2017;40(5):1504–1510. doi:10.3892/ijmm.2017.3150, PMID:28949386.
[126] Pellicoro A, Ramachandran P, Iredale JP, Fallowfield JA. Liver fibrosis and repair: immune regulation of wound healing in a solid organ. Nat Rev Immunol 2014;14(3):181–194. doi:10.1038/nri3623, PMID:24566915.
[127] Kong S, Kim SJ, Sandal B, Lee SM, Gao B, Zhang DD, *et al*. The type III histone deacetylase Sirt1 protein suppresses p300-mediated histone H3 lysine 56 acetylation at Bclaf1 promoter to inhibit T cell activation. J Biol Chem 2011;286(19):16967–16975. doi:10.1074/jbc.M111.218206, PMID:21454709.
[128] Li J, Zhang C, Hu Y, Peng J, Feng Q, Hu X. Nicotinamide enhances Treg differentiation by promoting Foxp3 acetylation in immune thrombocytopenia. Br J Haematol 2024;205(6):2432–2441. doi:10.1111/bjh.19820, PMID:39406393.
[129] Cai Y, Deng W, Yang Q, Pan G, Liang Z, Yang X, *et al*. High-fat diet-induced obesity causes intestinal Th17/Treg imbalance that impairs the intestinal barrier and aggravates anxiety-like behavior in mice. Int Immunopharmacol 2024;130:111783. doi:10.1016/j.intimp.2024.111783, PMID:38514921.
[130] Barrow F, Khan S, Fredrickson G, Wang H, Dietsche K, Parthiban P, *et al*. Microbiota-Driven Activation of Intrahepatic B Cells Aggravates NASH Through Innate and Adaptive Signaling. Hepatology 2021;74(2):704–722. doi:10.1002/hep.31755, PMID:33609303.
[131] Brockmann L, Tran A, Huang Y, Edwards M, Ronda C, Wang HH, *et al*. Intestinal microbiota-specific Th17 cells possess regulatory properties and suppress effector T cells via c-MAF and IL-10. Immunity 2023;56(12):2719–2735.e7. doi:10.1016/j.immuni.2023.11.003, PMID:38039966.
[132] Chen S, Guo H, Xie M, Zhou C, Zheng M. Neutrophil: An emerging player in the occurrence and progression of metabolic associated fatty liver disease. Int Immunopharmacol 2021;97:107609. doi:10.1016/j.intimp.2021.107609, PMID:33887577.
[133] Yang H, Wang H, Andersson U. Targeting Inflammation Driven by HMGB1. Front Immunol 2020;11:484. doi:10.3389/fimmu.2020.00484, PMID:32265930.
[134] Rahmani M, Nkwocha J, Hawkins E, Pei X, Parker RE, Kmieciak M, *et al*. Cotargeting BCL-2 and PI3K Induces BAX-Dependent Mitochondrial Apoptosis in AML Cells. Cancer Res 2018;78(11):3075–3086. doi:10.1158/0008-5472.CAN-17-3024, PMID:29559471.
[135] Shukla S, Sharma A, Pandey VK, Raisuddin S, Kakkar P. Concurrent acetylation of FoxO1/3a and p53 due to sirtuins inhibition elicit Bim/PUMA mediated mitochondrial dysfunction and apoptosis in berberine-treated HepG2 cells. Toxicol Appl Pharmacol 2016;291:70–83. doi:10.1016/j.taap.2015.12.006, PMID:26712469.
[136] Ryu J, Kim E, Kang MK, Song DG, Shin EA, Lee H, *et al*. Differential TM4SF5-mediated SIRT1 modulation and metabolic signaling in nonalcoholic steatohepatitis progression. J Pathol 2021;253(1):55–67. doi:10.1002/path.5548, PMID:32918742.
[137] Zhang S, Gang X, Yang S, Cui M, Sun L, Li Z, *et al*. The Alterations in and the Role of the Th17/Treg Balance in Metabolic Diseases. Front Immunol 2021;12:678355. doi:10.3389/fimmu.2021.678355, PMID:34322117.
[138] Coll RC, Schroder K, Pelegrín P. NLRP3 and pyroptosis blockers for treating inflammatory diseases. Trends Pharmacol Sci 2022;43(8):653–668. doi:10.1016/j.tips.2022.04.003, PMID:35513901.
[139] Yang S, Zou Y, Zhong C, Zhou Z, Peng X, Tang C. Dual role of pyroptosis in liver diseases: mechanisms, implications, and therapeutic perspectives. Front Cell Dev Biol 2025;13:1522206. doi:10.3389/fcell.2025.1522206, PMID:39917567.
[140] de Carvalho Ribeiro M, Szabo G. Role of the Inflammasome in Liver Disease. Annu Rev Pathol 2022;17:345–365. doi:10.1146/annurev-pathmechdis-032521-102529, PMID:34752711.
[141] Zhao R, Guo Z, Lu K, Chen Q, Riaz F, Zhou Y, *et al*. Hepatocyte-specific NR5A2 deficiency induces pyroptosis and exacerbates non-alcoholic steatohepatitis by downregulating ALDH1B1 expression. Cell Death Dis 2024;15(10):770. doi:10.1038/s41419-024-07151-1, PMID:39438459.
[142] Gaul S, Leszczynska A, Alegre F, Kaufmann B, Johnson CD, Adams LA, *et al*. Hepatocyte pyroptosis and release of inflammasome particles induce stellate cell activation and liver fibrosis. J Hepatol 2021;74(1):156–167. doi:10.1016/j.jhep.2020.07.041, PMID:32763266.
[143] Barra NG, Henriksbo BD, Anhê FF, Schertzer JD. The NLRP3 inflammasome regulates adipose tissue metabolism. Biochem J 2020;477(6):1089–1107. doi:10.1042/BCJ20190472, PMID:32202638.
[144] Hao YY, Cui WW, Gao HL, Wang MY, Liu Y, Li CR, *et al*. Jinlida granules ameliorate the high-fat-diet induced liver injury in mice by antagonising hepatocytes pyroptosis. Pharm Biol 2022;60(1):274–281. doi:10.1080/13880209.2022.2029501, PMID:35138995.
[145] Yu P, Zhang X, Liu N, Tang L, Peng C, Chen X. Pyroptosis: mechanisms and diseases. Signal Transduct Target Ther 2021;6(1):128. doi:10.1038/s41392-021-00507-5, PMID:33776057.
[146] Bertheloot D, Latz E, Franklin BS. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. Cell Mol Immunol 2021;18(5):1106–1121. doi:10.1038/s41423-020-00630-3, PMID:33785842.
[147] Xu B, Jiang M, Chu Y, Wang W, Chen D, Li X, *et al*. Gasdermin D plays a key role as a pyroptosis executor of non-alcoholic steatohepatitis in humans and mice. J Hepatol 2018;68(4):773–782. doi:10.1016/j.jhep.2017.11.040, PMID:29273476.
[148] Li YF, Nanayakkara G, Sun Y, Li X, Wang L, Cueto R, *et al*. Analyses of caspase-1-regulated transcriptomes in various tissues lead to identification of novel IL-1β-, IL-18- and sirtuin-1-independent pathways. J Hematol Oncol 2017;10(1):40. doi:10.1186/s13045-017-0406-2, PMID:28153032.
[149] Han H, Li J, Tian L, Pei L, Zheng M. Through regulation of the SIRT1 pathway plant sterol ester of α-linolenic acid inhibits pyroptosis thereby attenuating the development of NASH in mice. J Nutr Biochem 2023;119:109408. doi:10.1016/j.jnutbio.2023.109408, PMID:37336331.
[150] Kuang G, Zhao Y, Wang L, Wen T, Liu P, Ma B, *et al*. Astragaloside IV Alleviates Acute Hepatic Injury by Regulating Macrophage Polarization and Pyroptosis via Activation of the AMPK/SIRT1 Signaling Pathway. Phytother Res 2025;39(2):733–746. doi:10.1002/ptr.8403, PMID:39660635.
[151] Niazpour F, Meshkani R. Unlocking the Therapeutic Potential of Autophagy Modulation by Natural Products in Tackling Non-Alcoholic Fatty Liver Disease. Phytother Res 2025;39(5):2357–2373. doi:10.1002/ptr.8463, PMID:40184168.
[152] Ma YN, Jiang X, Tang W, Song P. Influence of intermittent fasting on autophagy in the liver. Biosci Trends 2023;17(5):335–355. doi:10.5582/bst.2023.01207, PMID:37661370.
[153] Byrnes K, Blessinger S, Bailey NT, Scaife R, Liu G, Khambu B. Therapeutic regulation of autophagy in hepatic metabolism. Acta Pharm Sin B 2022;12(1):33–49. doi:10.1016/j.apsb.2021.07.021, PMID:35127371.
[154] Chen CL, Lin YC. Autophagy Dysregulation in Metabolic Associated Fatty Liver Disease: A New Therapeutic Target. Int J Mol Sci 2022;23(17):10055. doi:10.3390/ijms231710055, PMID:36077452.
[155] Xie W, Zhu T, Zhang S, Sun X. Protective effects of Gypenoside XVII against cerebral ischemia/reperfusion injury via SIRT1-FOXO3A- and Hif1a-BNIP3-mediated mitochondrial autophagy. J Transl Med 2022;20(1):622. doi:10.1186/s12967-022-03830-9, PMID:36572901.
[156] El-Ashmawy NE, Al-Ashmawy GM, Kamel AA, Khedr EG. Unlocking the therapeutic potential of canagliflozin in NAFLD: Insights into AMPK/SIRT1-mediated lipophagy. Biochim Biophys Acta Mol Basis Dis 2025;1871(3):167666. doi:10.1016/j.bbadis.2025.167666, PMID:39837063.
[157] Grefhorst A, van de Peppel IP, Larsen LE, Jonker JW, Holleboom AG. The Role of Lipophagy in the Development and Treatment of Non-Alcoholic Fatty Liver Disease. Front Endocrinol (Lausanne) 2020;11:601627. doi:10.3389/fendo.2020.601627, PMID:33597924.
[158] Xiong J, Chen G, He Y, Zhao C, Chen D, Liu Y, *et al*. Oxymatrine reduces hepatic lipid synthesis in rat model of nonalcoholic steatohepatitis by regulating Sirt1/AMPK and LXR/Plin2/SREBP-1c pathways. Chem Biol Interact 2025;407:111370. doi:10.1016/j.cbi.2024.111370, PMID:39746502.
[159] Lebeaupin C, Vallée D, Hazari Y, Hetz C, Chevet E, Bailly-Maitre B. Endoplasmic reticulum stress signalling and the pathogenesis of non-alcoholic fatty liver disease. J Hepatol 2018;69(4):927–947. doi:10.1016/j.jhep.2018.06.008, PMID:29940269.
[160] Zhao Y, Li HX, Luo Y, Cui JG, Talukder M, Li JL. Lycopene mitigates DEHP-induced hepatic mitochondrial quality control disorder via regulating SIRT1/PINK1/mitophagy axis and mitochondrial unfolded protein response. Environ Pollut 2022;292(Pt B):118390. doi:10.1016/j.envpol.2021.118390, PMID:34699919.
[161] Zhao K, Zhang H, Yang D. SIRT1 exerts protective effects by inhibiting endoplasmic reticulum stress and NF-κB signaling pathways. Front Cell Dev Biol 2024;12:1405546. doi:10.3389/fcell.2024.1405546, PMID:38745862.
[162] Mochida K, Nakatogawa H. ER-phagy: selective autophagy of the endoplasmic reticulum. EMBO Rep 2022;23(8):e55192. doi:10.15252/embr.202255192, PMID:35758175.
[163] Kim YS, Kim SG. Endoplasmic reticulum stress and autophagy dysregulation in alcoholic and non-alcoholic liver diseases. Clin Mol Hepatol 2020;26(4):715–727. doi:10.3350/cmh.2020.0173, PMID:32951410.
[164] Marqués P, Burillo J, González-Blanco C, Jiménez B, García G, García-Aguilar A, *et al*. Regulation of TSC2 lysosome translocation and mitochondrial turnover by TSC2 acetylation status. Sci Rep 2024;14(1):12521. doi:10.1038/s41598-024-63525-7, PMID:38822085.
[165] Wang F, Jia J, Rodrigues B. Autophagy, Metabolic Disease, and Pathogenesis of Heart Dysfunction. Can J Cardiol 2017;33(7):850–859. doi:10.1016/j.cjca.2017.01.002, PMID:28389131.
[166] Cao Y, Mai W, Li R, Deng S, Li L, Zhou Y, *et al*. Macrophages evoke autophagy of hepatic stellate cells to promote liver fibrosis in NAFLD mice via the PGE2/EP4 pathway. Cell Mol Life Sci 2022;79(6):303. doi:10.1007/s00018-022-04319-w, PMID:35588334.
[167] Clare K, Dillon JF, Brennan PN. Reactive Oxygen Species and Oxidative Stress in the Pathogenesis of MAFLD. J Clin Transl Hepatol 2022;10(5):939–946. doi:10.14218/JCTH.2022.00067, PMID:36304513.
[168] Zheng Y, Wang S, Wu J, Wang Y. Mitochondrial metabolic dysfunc-

tion and non-alcoholic fatty liver disease: new insights from pathogenic mechanisms to clinically targeted therapy. J Transl Med 2023;21(1):510. doi:10.1186/s12967-023-04367-1, PMID:37507803.
[169] Singh CK, Chhabra G, Ndiaye MA, Garcia-Peterson LM, Mack NJ, Ahmad N. The Role of Sirtuins in Antioxidant and Redox Signaling. Antioxid Redox Signal 2018;28(8):643–661. doi:10.1089/ars.2017.7290, PMID:28891317.
[170] Jiang H, Mao T, Sun Z, Shi L, Han X, Zhang Y, *et al*. Yinchen Linggui Zhugan decoction ameliorates high fat diet-induced nonalcoholic fatty liver disease by modulation of SIRT1/Nrf2 signaling pathway and gut microbiota. Front Microbiol 2022;13:1001778. doi:10.3389/fmicb.2022.1001778, PMID:36578580.
[171] Hou Y, Fan F, Xie N, Zhang Y, Wang X, Meng X. Rhodiola crenulata alleviates hypobaric hypoxia-induced brain injury by maintaining BBB integrity and balancing energy metabolism dysfunction. Phytomedicine 2024;128:155529. doi:10.1016/j.phymed.2024.155529, PMID:38503156.
[172] Cui Z, Zhao X, Amevor FK, Du X, Wang Y, Li D, *et al*. Therapeutic application of quercetin in aging-related diseases: SIRT1 as a potential mechanism. Front Immunol 2022;13:943321. doi:10.3389/fimmu.2022.943321, PMID:35935939.
[173] Lin CH, Jiang WP, Itokazu N, Huang GJ. Chlorogenic acid attenuates 5-fluorouracil-induced intestinal mucositis in mice through SIRT1 signaling-mediated oxidative stress and inflammatory pathways. Biomed Pharmacother 2025;186:117982. doi:10.1016/j.biopha.2025.117982, PMID:40106967.
[174] Zhang J, Hu C, Li X, Liang L, Zhang M, Chen B, *et al*. Protective Effect of Dihydrokaempferol on Acetaminophen-Induced Liver Injury by Activating the SIRT1 Pathway. Am J Chin Med 2021;49(3):705–718. doi:10.1142/S0192415X21500324, PMID:33657990.
[175] Abu Shelbayeh O, Arroum T, Morris S, Busch KB. PGC-1α Is a Master Regulator of Mitochondrial Lifecycle and ROS Stress Response. Antioxidants (Basel) 2023;12(5):1075. doi:10.3390/antiox12051075, PMID:37237941.
[176] Li W, Cai Z, Schindler F, Afjehi-Sadat L, Montsch B, Heffeter P, *et al*. Elevated PINK1/Parkin-Dependent Mitophagy and Boosted Mitochondrial Function Mediate Protection of HepG2 Cells from Excess Palmitic Acid by Hesperetin. J Agric Food Chem 2024;72(23):13039–13053. doi:10.1021/acs.jafc.3c09132, PMID:38809522.
[177] Singh V, Ubaid S. Role of Silent Information Regulator 1 (SIRT1) in Regulating Oxidative Stress and Inflammation. Inflammation 2020;43(5):1589–1598. doi:10.1007/s10753-020-01242-9, PMID:32410071.
[178] Zeng C, Chen M. Progress in Nonalcoholic Fatty Liver Disease: SIRT Family Regulates Mitochondrial Biogenesis. Biomolecules 2022;12(8):1079. doi:10.3390/biom12081079, PMID:36008973.
[179] Chini CCS, Cordeiro HS, Tran NLK, Chini EN. NAD metabolism: Role in senescence regulation and aging. Aging Cell 2024;23(1):e13920. doi:10.1111/acel.13920, PMID:37424179.
[180] Dong W, Zhu X, Liu X, Zhao X, Lei X, Kang L, *et al*. Role of the SENP1-SIRT1 pathway in hyperoxia-induced alveolar epithelial cell injury. Free Radic Biol Med 2021;173:142–150. doi:10.1016/j.freeradbiomed.2021.07.027, PMID:34311030.
[181] Zhang M, Xue X, Lou Z, Lin Y, Li Q, Huang C. Exosomes from senescent epithelial cells activate pulmonary fibroblasts via the miR-217-5p/Sirt1 axis in paraquat-induced pulmonary fibrosis. J Transl Med 2024;22(1):310. doi:10.1186/s12967-024-05094-x, PMID:38532482.
[182] Zhan T, Chen Y, Dong L, Wei T, Lu D, Wang Q, *et al*. Nicotinamide phosphoribose transferase facilitates macrophage-mediated pulmonary fibrosis through the Sirt1-Smad7 pathway in mice. Eur J Pharmacol 2024;967:176355. doi:10.1016/j.ejphar.2024.176355, PMID:38280463.
[183] Jiang J, Gao Y, Wang J, Huang Y, Yang R, Zhang Y, *et al*. Hepatic sphingomyelin phosphodiesterase 3 promotes steatohepatitis by disrupting membrane sphingolipid metabolism. Cell Metab 2025;37(5):1119–1136.e13. doi:10.1016/j.cmet.2025.01.016, PMID:40015281.
[184] Sharma A, Chabloz S, Lapides RA, Roider E, Ewald CY. Potential Synergistic Supplementation of NAD+ Promoting Compounds as a Strategy for Increasing Healthspan. Nutrients 2023;15(2):445. doi:10.3390/nu15020445, PMID:36678315.
[185] Sun H, Li D, Wei C, Liu L, Xin Z, Gao H, *et al*. The relationship between SIRT1 and inflammation: a systematic review and meta-analysis. Front Immunol 2024;15:1465849. doi:10.3389/fimmu.2024.1465849, PMID:39676853.
[186] Tilg H, Adolph TE, Trauner M. Gut-liver axis: Pathophysiological concepts and clinical implications. Cell Metab 2022;34(11):1700–1718. doi:10.1016/j.cmet.2022.09.017, PMID:36208625.
[187] Ling C, Versloot CJ, Arvidsson Kvissberg ME, Hu G, Swain N, Horcas-Nieto JM, *et al*. Rebalancing of mitochondrial homeostasis through an NAD(+)-SIRT1 pathway preserves intestinal barrier function in severe malnutrition. EBioMedicine 2023;96:104809. doi:10.1016/j.ebiom.2023.104809, PMID:37738832.
[188] Wu L, Chen Q, Dong B, Geng H, Wang Y, Han D, *et al*. Resveratrol alleviates lipopolysaccharide-induced liver injury by inducing SIRT1/P62-mediated mitophagy in gibel carp (Carassius gibelio). Front Immunol 2023;14:1177140. doi:10.3389/fimmu.2023.1177140, PMID:37168854.
[189] Li X, Cui J, Ding Z, Tian Z, Kong Y, Li L, *et al*. Klebsiella pneumoniae-derived extracellular vesicles impair endothelial function by inhibiting SIRT1. Cell Commun Signal 2025;23(1):21. doi:10.1186/s12964-024-02002-0, PMID:39800699.
[190] Ruan D, Wu S, Fouad AM, Zhu Y, Huang W, Chen Z, *et al*. Curcumin alleviates LPS-induced intestinal homeostatic imbalance through reshaping gut microbiota structure and regulating group 3 innate lymphoid cells in chickens. Food Funct 2022;13(22):11811–11824. doi:10.1039/d2fo02598a, PMID:36306140.
[191] Cui S, Hu H, Chen A, Cui M, Pan X, Zhang P, *et al*. SIRT1 activation synergizes with FXR agonism in hepatoprotection via governing nucleocytoplasmic shuttling and degradation of FXR. Acta Pharm Sin B 2023;13(2):559–576. doi:10.1016/j.apsb.2022.08.019, PMID:36873184.
[192] Qin T, Hasnat M, Wang Z, Hassan HM, Zhou Y, Yuan Z, *et al*. Geniposide alleviated bile acid-associated NLRP3 inflammasome activation by regulating SIRT1/FXR signaling in bile duct ligation-induced liver fibrosis. Phytomedicine 2023;118:154971. doi:10.1016/j.phymed.2023.154971, PMID:37494875.
[193] Lai J, Li F, Li H, Huang R, Ma F, Gu X, *et al*. Melatonin alleviates necrotizing enterocolitis by reducing bile acid levels through the SIRT1/FXR signalling axis. Int Immunopharmacol 2024;128:111360. doi:10.1016/j.intimp.2023.111360, PMID:38176339.
[194] Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. Cell Metab 2018;27(4):740–756. doi:10.1016/j.cmet.2018.03.001, PMID:29617641.
[195] Zhang H, Zhao X, Zhang L, Sun D, Ma Y, Bai Y, *et al*. Nicotinamide Riboside Ameliorates Fructose-Induced Lipid Metabolism Disorders in Mice by Activating Browning of WAT, and May Be Also Related to the Regulation of Gut Microbiota. Nutrients 2024;16(22):3920. doi:10.3390/nu16223920, PMID:39599706.
[196] Chopyk DM, Grakoui A. Contribution of the Intestinal Microbiome and Gut Barrier to Hepatic Disorders. Gastroenterology 2020;159(3):849–863. doi:10.1053/j.gastro.2020.04.077, PMID:32569766.
[197] Yang N, Sun R, Zhang X, Wang J, Wang L, Zhu H, *et al*. Alternative pathway of bile acid biosynthesis contributes to ameliorate NASH after induction of NAMPT/NAD(+)/SIRT1 axis. Biomed Pharmacother 2023;164:114987. doi:10.1016/j.biopha.2023.114987, PMID:37315437.
[198] Chen X, Xuan Y, Chen Y, Yang F, Zhu M, Xu J, *et al*. Polystyrene nanoplastics induce intestinal and hepatic inflammation through activation of NF-κB/NLRP3 pathways and related gut-liver axis in mice. Sci Total Environ 2024;935:173458. doi:10.1016/j.scitotenv.2024.173458, PMID:38796000.
[199] Nawrot M, Peschard S, Lestavel S, Staels B. Intestine-liver crosstalk in Type 2 Diabetes and non-alcoholic fatty liver disease. Metabolism 2021;123:154844. doi:10.1016/j.metabol.2021.154844, PMID:34343577.
[200] Lang S, Schnabl B. Microbiota and Fatty Liver Disease-the Known, the Unknown, and the Future. Cell Host Microbe 2020;28(2):233–244. doi:10.1016/j.chom.2020.07.007, PMID:32791115.
[201] Matenchuk BA, Mandhane PJ, Kozyrskyj AL. Sleep, circadian rhythm, and gut microbiota. Sleep Med Rev 2020;53:101340. doi:10.1016/j.smrv.2020.101340, PMID:32668369.
[202] Kim KE, Kim H, Heo RW, Shin HJ, Yi CO, Lee DH, *et al*. Myeloid-specific SIRT1 Deletion Aggravates Hepatic Inflammation and Steatosis in High-fat Diet-fed Mice. Korean J Physiol Pharmacol 2015;19(5):451–460. doi:10.4196/kjpp.2015.19.5.451, PMID:26330758.
[203] Sharma S, Gali S, Kundu A, Park JH, Kim JS, Kim HS. Tenovin-1, a Selective SIRT1/2 Inhibitor, Attenuates High-fat Diet-induced Hepatic Fibrosis via Inhibition of HSC Activation in ZDF Rats. Int J Biol Sci 2024;20(9):3334–3352. doi:10.7150/ijbs.97304, PMID:38993557.
[204] Yang X, Lu D, Zhuo J, Lin Z, Yang M, Xu X. The Gut-liver Axis in Immune Remodeling: New insight into Liver Diseases. Int J Biol Sci 2020;16(13):2357–2366. doi:10.7150/ijbs.46405, PMID:32760203.
[205] Dai H, Sinclair DA, Ellis JL, Steegborn C. Sirtuin activators and inhibitors: Promises, achievements, and challenges. Pharmacol Ther 2018;188:140–154. doi:10.1016/j.pharmthera.2018.03.004, PMID:29577959.
[206] Fraga CG, Croft KD, Kennedy DO, Tomás-Barberán FA. The effects of polyphenols and other bioactives on human health. Food Funct 2019;10(2):514–528. doi:10.1039/c8fo01997e, PMID:30746536.
[207] Iside C, Scafuro M, Nebbioso A, Altucci L. SIRT1 Activation by Natural Phytochemicals: An Overview. Front Pharmacol 2020;11:1225. doi:10.3389/fphar.2020.01225, PMID:32848804.
[208] Wiciński M, Erdmann J, Nowacka A, Kuźmiński O, Michalak K, Janowski K, *et al*. Natural Phytochemicals as SIRT Activators-Focus on Potential Biochemical Mechanisms. Nutrients 2023;15(16):3578. doi:10.3390/nu15163578, PMID:37630770.
[209] Zhang LX, Li CX, Kakar MU, Khan MS, Wu PF, Amir RM, *et al*. Resveratrol (RV): A pharmacological review and call for further research. Biomed Pharmacother 2021;143:112164. doi:10.1016/j.biopha.2021.112164, PMID:34649335.
[210] Kim OY, Chung JY, Song J. Effect of resveratrol on adipokines and myokines involved in fat browning: Perspectives in healthy weight against obesity. Pharmacol Res 2019;148:104411. doi:10.1016/j.phrs.2019.104411, PMID:31449976.
[211] Shahcheraghi SH, Salemi F, Small S, Syed S, Salari F, Alam W, *et al*. Resveratrol regulates inflammation and improves oxidative stress via Nrf2 signaling pathway: Therapeutic and biotechnological prospects. Phytother Res 2023;37(4):1590–1605. doi:10.1002/ptr.7754, PMID:36752350.
[212] Sikur N, Böröczky C, Paszternák A, Gyöngyössy R, Szőkő É, Varga K, *et al*. Resveratrol and Its Derivatives Diminish Lipid Accumulation in Adipocytes In Vitro-Mechanism of Action and Structure-Activity Relationship. Nutrients 2024;16(22):3869. doi:10.3390/nu16223869, PMID:39599655.
[213] Rafiei H, Omidian K, Bandy B. Dietary Polyphenols Protect Against Oleic Acid-Induced Steatosis in an in Vitro Model of NAFLD by Modulating Lipid Metabolism and Improving Mitochondrial Function. Nutrients 2019;11(3):541. doi:10.3390/nu11030541, PMID:30832407.
[214] Meng T, Xiao D, Muhammed A, Deng J, Chen L, He J. Anti-Inflammatory Action and Mechanisms of Resveratrol. Molecules 2021;26(1):229. doi:10.3390/molecules26010229, PMID:33466247.
[215] Wang P, Gao J, Ke W, Wang J, Li D, Liu R, *et al*. Resveratrol reduces obesity in high-fat diet-fed mice via modulating the composition and metabolic function of the gut microbiota. Free Radic Biol Med 2020;156:83–98.

doi:10.1016/j.freeradbiomed.2020.04.013, PMID:32305646.
[216] Yang Y, Sun Y, Gu T, Yan Y, Guo J, Zhang X, *et al*. The Metabolic Characteristics and Bioavailability of Resveratrol Based on Metabolic Enzymes. Nutr Rev 2025;83(4):749–770. doi:10.1093/nutrit/nuae161, PMID:39520710.
[217] Fu YS, Chen TH, Weng L, Huang L, Lai D, Weng CF. Pharmacological properties and underlying mechanisms of curcumin and prospects in medicinal potential. Biomed Pharmacother 2021;141:111888. doi:10.1016/j.biopha.2021.111888, PMID:34237598.
[218] Zendedel E, Butler AE, Atkin SL, Sahebkar A. Impact of curcumin on sirtuins: A review. J Cell Biochem 2018;119(12):10291–10300. doi:10.1002/jcb.27371, PMID:30145851.
[219] Ma PY, Li XY, Wang YL, Lang DQ, Liu L, Yi YK, *et al*. Natural bioactive constituents from herbs and nutraceuticals promote browning of white adipose tissue. Pharmacol Res 2022;178:106175. doi:10.1016/j.phrs.2022.106175, PMID:35283301.
[220] Peng X, Dai C, Liu Q, Li J, Qiu J. Curcumin Attenuates on Carbon Tetrachloride-Induced Acute Liver Injury in Mice via Modulation of the Nrf2/HO-1 and TGF-β1/Smad3 Pathway. Molecules 2018;23(1):215. doi:10.3390/molecules23010215, PMID:29351226.
[221] Huang Y, Zhan Y, Luo G, Zeng Y, McClements DJ, Hu K. Curcumin encapsulated zein/caseinate-alginate nanoparticles: Release and antioxidant activity under in vitro simulated gastrointestinal digestion. Curr Res Food Sci 2023;6:100463. doi:10.1016/j.crfs.2023.100463, PMID:36860615.
[222] Unhapipatpong C, Polruang N, Shantavasinkul PC, Julanon N, Numthavaj P, Thakkinstian A. The effect of curcumin supplementation on weight loss and anthropometric indices: an umbrella review and updated meta-analyses of randomized controlled trials. Am J Clin Nutr 2023;117(5):1005–1016. doi:10.1016/j.ajcnut.2023.03.006, PMID:36898635.
[223] Chang R, Chen L, Qamar M, Wen Y, Li L, Zhang J, *et al*. The bioavailability, metabolism and microbial modulation of curcumin-loaded nanodelivery systems. Adv Colloid Interface Sci 2023;318:102933. doi:10.1016/j.cis.2023.102933, PMID:37301064.
[224] Kashyap D, Garg VK, Tuli HS, Yerer MB, Sak K, Sharma AK, *et al*. Fisetin and Quercetin: Promising Flavonoids with Chemopreventive Potential. Biomolecules 2019;9(5):174. doi:10.3390/biom9050174, PMID:31064104.
[225] Hosseini A, Razavi BM, Banach M, Hosseinzadeh H. Quercetin and metabolic syndrome: A review. Phytother Res 2021;35(10):5352–5364. doi:10.1002/ptr.7144, PMID:34101925.
[226] Tan Y, Tam CC, Rolston M, Alves P, Chen L, Meng S, *et al*. Quercetin Ameliorates Insulin Resistance and Restores Gut Microbiome in Mice on High-Fat Diets. Antioxidants (Basel) 2021;10(8):1251. doi:10.3390/antiox10081251, PMID:34439499.
[227] Yang H, Yang T, Heng C, Zhou Y, Jiang Z, Qian X, *et al*. Quercetin improves nonalcoholic fatty liver by ameliorating inflammation, oxidative stress, and lipid metabolism in db/db mice. Phytother Res 2019;33(12):3140–3152. doi:10.1002/ptr.6486, PMID:31452288.
[228] Katsaros I, Sotiropoulou M, Vailas M, Kapetanakis EI, Valsami G, Tsaroucha A, *et al*. Quercetin's Potential in MASLD: Investigating the Role of Autophagy and Key Molecular Pathways in Liver Steatosis and Inflammation. Nutrients 2024;16(22):3789. doi:10.3390/nu16223789, PMID:39599578.
[229] Huang H, Liao D, Dong Y, Pu R. Effect of quercetin supplementation on plasma lipid profiles, blood pressure, and glucose levels: a systematic review and meta-analysis. Nutr Rev 2020;78(8):615–626. doi:10.1093/nutrit/nuz071, PMID:31940027.
[230] Natraj P, Rajan P, Jeon YA, Kim SS, Lee YJ. Antiadipogenic Effect of Citrus Flavonoids: Evidence from RNA Sequencing Analysis and Activation of AMPK in 3T3-L1 Adipocytes. J Agric Food Chem 2023;71(46):17788–17800. doi:10.1021/acs.jafc.3c03559, PMID:37955544.
[231] Lin X, Kong LN, Huang C, Ma TT, Meng XM, He Y, *et al*. Hesperetin derivative-7 inhibits PDGF-BB-induced hepatic stellate cell activation and proliferation by targeting Wnt/β-catenin pathway. Int Immunopharmacol 2015;25(2):311–320. doi:10.1016/j.intimp.2015.02.009, PMID:25701506.
[232] Gou F, Lin Q, Tu X, Zhu J, Li X, Chen S, *et al*. Hesperidin Alleviated Intestinal Barrier Injury, Mitochondrial Dysfunction, and Disorder of Endoplasmic Reticulum Mitochondria Contact Sites under Oxidative Stress. J Agric Food Chem 2024;72(29):16276–16286. doi:10.1021/acs.jafc.4c02265, PMID:38981046.
[233] Zhang M, Ge T, Huang W, He J, Huang C, Ou J, *et al*. Formation of Hesperetin-Methylglyoxal Adducts in Food and In Vivo, and Their Metabolism In Vivo and Potential Health Impacts. J Agric Food Chem 2024;72(19):11174–11184. doi:10.1021/acs.jafc.4c00481, PMID:38687489.
[234] Fernandes R, Medrano-Padial C, Dias-Costa R, Domínguez-Perles R, Botelho C, Fernandes R, *et al*. Grape stems as sources of tryptophan and selenium: Functional properties and antioxidant potential. Food Chem X 2025;26:102260. doi:10.1016/j.fochx.2025.102260, PMID:39995406.
[235] He L, Yang G, Li T, Li W, Yang R. Metabolic profile of procyanidin A2 by human intestinal microbiota and their antioxidant and hypolipidemic potential in HepG2 cells. Eur J Nutr 2025;64(3):113. doi:10.1007/s00394-025-03638-5, PMID:40056191.
[236] Sun B, Wang Y, Bai J, Li X, Ma L, Man S. Litchi Procyanidins Ameliorate DSS-Induced Colitis through Gut Microbiota-Dependent Regulation of Treg/Th17 Balance. J Agric Food Chem 2024;72(44):24823–24832. doi:10.1021/acs.jafc.4c05577, PMID:39315595.
[237] Cao P, Zhang Y, Huang Z, Sullivan MA, He Z, Wang J, *et al*. The Preventative Effects of Procyanidin on Binge Ethanol-Induced Lipid Accumulation and ROS Overproduction via the Promotion of Hepatic Autophagy. Mol Nutr Food Res 2019;63(18):e1801255. doi:10.1002/mnfr.201801255, PMID:31336037.
[238] Saqib U, Kelley TT, Panguluri SK, Liu D, Savai R, Baig MS, *et al*. Polypharmacology or Promiscuity? Structural Interactions of Resveratrol With Its Bandwagon of Targets. Front Pharmacol 2018;9:1201. doi:10.3389/fphar.2018.01201, PMID:30405416.
[239] Steg A, Oczkowicz M, Smołucha G. Omics as a Tool to Help Determine the Effectiveness of Supplements. Nutrients 2022;14(24):5305. doi:10.3390/nu14245305, PMID:36558464.
[240] Bai X, Yao L, Ma X, Xu X. Small Molecules as SIRT Modulators. Mini Rev Med Chem 2018;18(13):1151–1157. doi:10.2174/1389557516666160620095103, PMID:27334466.
[241] Yap KH, Yee GS, Candasamy M, Tan SC, Md S, Abdul Majeed AB, *et al*. Catalpol Ameliorates Insulin Sensitivity and Mitochondrial Respiration in Skeletal Muscle of Type-2 Diabetic Mice Through Insulin Signaling Pathway and AMPK/SIRT1/PGC-1α/PPAR-γ Activation. Biomolecules 2020;10(10):1360. doi:10.3390/biom10101360, PMID:32987623.
[242] Elmorsy EA, Elsisi HA, Alkhamiss AS, Alsoqih NS, Khodeir MM, Alsalloom AA, *et al*. Activation of SIRT1 by SRT1720 alleviates dyslipidemia, improves insulin sensitivity and exhibits liver-protective effects in diabetic rats on a high-fat diet: New insights into the SIRT1/Nrf2/NFκB signaling pathway. Eur J Pharm Sci 2025;206:107002. doi:10.1016/j.ejps.2025.107002, PMID:39778687.
[243] Zhang Y, Li Y, Li J, Li B, Chong Y, Zheng G, *et al*. SIRT1 alleviates isoniazid-induced hepatocyte injury by reducing histone acetylation in the IL-6 promoter region. Int Immunopharmacol 2019;67:348–355. doi:10.1016/j.intimp.2018.11.054, PMID:30578970.
[244] Hoffmann E, Wald J, Lavu S, Roberts J, Beaumont C, Haddad J, *et al*. Pharmacokinetics and tolerability of SRT2104, a first-in-class small molecule activator of SIRT1, after single and repeated oral administration in man. Br J Clin Pharmacol 2013;75(1):186–196. doi:10.1111/j.1365-2125.2012.04340.x, PMID:22616762.
[245] Wesolowski LT, Simons JL, Semanchik PL, Othman MA, Kim JH, Lawler JM, *et al*. The Impact of SRT2104 on Skeletal Muscle Mitochondrial Function, Redox Biology, and Loss of Muscle Mass in Hindlimb Unloaded Rats. Int J Mol Sci 2023;24(13):11135. doi:10.3390/ijms241311135, PMID:37446313.
[246] Baksi A, Kraydashenko O, Zalevkaya A, Stets R, Elliott P, Haddad J, *et al*. A phase II, randomized, placebo-controlled, double-blind, multi-dose study of SRT2104, a SIRT1 activator, in subjects with type 2 diabetes. Br J Clin Pharmacol 2014;78(1):69–77. doi:10.1111/bcp.12327, PMID:24446723.
[247] Libri V, Brown AP, Gambarota G, Haddad J, Shields GS, Dawes H, *et al*. A pilot randomized, placebo controlled, double blind phase I trial of the novel SIRT1 activator SRT2104 in elderly volunteers. PLoS One 2012;7(12):e51395. doi:10.1371/journal.pone.0051395, PMID:23284689.
[248] Yaku K, Palikhe S, Iqbal T, Hayat F, Watanabe Y, Fujisaka S, *et al*. Nicotinamide riboside and nicotinamide mononucleotide facilitate NAD(+) synthesis via enterohepatic circulation. Sci Adv 2025;11(12):eadr1538. doi:10.1126/sciadv.adr1538, PMID:40117359.
[249] Yen BL, Wang LT, Wang HH, Hung CP, Hsu PJ, Chang CC, *et al*. Excess glucose alone depress young mesenchymal stromal/stem cell osteogenesis and mitochondria activity within hours/days via NAD(+)/SIRT1 axis. J Biomed Sci 2024;31(1):49. doi:10.1186/s12929-024-01039-0, PMID:38735943.
[250] Elmorsy EA, Elashry HA, Alkhamiss AS, Alsaykhan H, Hamad RS, Abdel-Reheim MA, *et al*. E1231/NMN protects against experimental metabolic syndrome: the central role of SIRT1 in modulating AKT/Nrf2/NFκB signaling. Front Pharmacol 2025;16:1558709. doi:10.3389/fphar.2025.1558709, PMID:40166461.
[251] Zhang Y, Chen ML, Zhou Y, Yi L, Gao YX, Ran L, *et al*. Resveratrol improves hepatic steatosis by inducing autophagy through the cAMP signaling pathway. Mol Nutr Food Res 2015;59(8):1443–1457. doi:10.1002/mnfr.201500016, PMID:25943029.
[252] Xu K, Liu S, Zhao X, Zhang X, Fu X, Zhou Y, *et al*. Treating hyperuricemia related non-alcoholic fatty liver disease in rats with resveratrol. Biomed Pharmacother 2019;110:844–849. doi:10.1016/j.biopha.2018.12.039, PMID:30557833.
[253] Tian Y, Ma J, Wang W, Zhang L, Xu J, Wang K, *et al*. Resveratrol supplement inhibited the NF-κB inflammation pathway through activating AMPKα-SIRT1 pathway in mice with fatty liver. Mol Cell Biochem 2016;422(1-2):75–84. doi:10.1007/s11010-016-2807-x, PMID:27613163.
[254] Du F, Huang R, Lin D, Wang Y, Yang X, Huang X, *et al*. Resveratrol Improves Liver Steatosis and Insulin Resistance in Non-alcoholic Fatty Liver Disease in Association With the Gut Microbiota. Front Microbiol 2021;12:611323. doi:10.3389/fmicb.2021.611323, PMID:33708180.
[255] Zhao G, Yang L, Zhong W, Hu Y, Tan Y, Ren Z, *et al*. Polydatin, A Glycoside of Resveratrol, Is Better Than Resveratrol in Alleviating Non-alcoholic Fatty Liver Disease in Mice Fed a High-Fructose Diet. Front Nutr 2022;9:857879. doi:10.3389/fnut.2022.857879, PMID:35651514.
[256] Chen Y, Zhang H, Chen Y, Zhang Y, Shen M, Jia P, *et al*. Resveratrol Alleviates Endoplasmic Reticulum Stress-Associated Hepatic Steatosis and Injury in Mice Challenged with Tunicamycin. Mol Nutr Food Res 2020;64(14):e2000105. doi:10.1002/mnfr.202000105, PMID:32529694.
[257] He Y, Wang H, Lin S, Chen T, Chang D, Sun Y, *et al*. Advanced effect of curcumin and resveratrol on mitigating hepatic steatosis in metabolic associated fatty liver disease via the PI3K/AKT/mTOR and HIF-1/VEGF cascade. Biomed Pharmacother 2023;165:115279. doi:10.1016/j.biopha.2023.115279, PMID:37544281.
[258] Lee DE, Lee SJ, Kim SJ, Lee HS, Kwon OS. Curcumin Ameliorates Nonalcoholic Fatty Liver Disease through Inhibition of O-GlcNAcylation. Nutrients 2019;11(11):2702. doi:10.3390/nu11112702, PMID:31717261.
[259] Sun Q, Niu Q, Guo Y, Zhuang Y, Li X, Liu J, *et al*. Regulation on Citrate Influx and Metabolism through Inhibiting SLC13A5 and ACLY: A Novel Mechanism Mediating the Therapeutic Effects of Curcumin on NAFLD. J Agric Food Chem 2021;69(31):8714–8725. doi:10.1021/acs.jafc.1c03105, PMID:34323067.

[260] Lee ES, Kwon MH, Kim HM, Woo HB, Ahn CM, Chung CH. Curcumin analog CUR5-8 ameliorates nonalcoholic fatty liver disease in mice with high-fat diet-induced obesity. Metabolism 2020;103:154015. doi:10.1016/j.metabol.2019.154015, PMID:31758951.
[261] Yan C, Zhang Y, Zhang X, Aa J, Wang G, Xie Y. Curcumin regulates endogenous and exogenous metabolism via Nrf2-FXR-LXR pathway in NAFLD mice. Biomed Pharmacother 2018;105:274–281. doi:10.1016/j.biopha.2018.05.135, PMID:29860219.
[262] Gao XR, Chen Z, Fang K, Xu JX, Ge JF. Protective effect of quercetin against the metabolic dysfunction of glucose and lipids and its associated learning and memory impairments in NAFLD rats. Lipids Health Dis 2021;20(1):164. doi:10.1186/s12944-021-01590-x, PMID:34789244.
[263] Juárez-Fernández M, Porras D, Petrov P, Román-Sagüillo S, García-Mediavilla MV, Soluyanova P, *et al*. The Synbiotic Combination of Akkermansia muciniphila and Quercetin Ameliorates Early Obesity and NAFLD through Gut Microbiota Reshaping and Bile Acid Metabolism Modulation. Antioxidants (Basel) 2021;10(12):2001. doi:10.3390/antiox10122001, PMID:34943104.
[264] Yang T, Wang Y, Cao X, Peng Y, Huang J, Chen L, *et al*. Targeting mTOR/YY1 signaling pathway by quercetin through CYP7A1-mediated cholesterol-to-bile acids conversion alleviated type 2 diabetes mellitus induced hepatic lipid accumulation. Phytomedicine 2023;113:154703. doi:10.1016/j.phymed.2023.154703, PMID:36889164.
[265] Jiang JJ, Zhang GF, Zheng JY, Sun JH, Ding SB. Targeting Mitochondrial ROS-Mediated Ferroptosis by Quercetin Alleviates High-Fat Diet-Induced Hepatic Lipotoxicity. Front Pharmacol 2022;13:876550. doi:10.3389/fphar.2022.876550, PMID:35496312.
[266] Shi Z, Zhang C, Lei H, Chen C, Cao Z, Song Y, *et al*. Structural Insights into Amelioration Effects of Quercetin and Its Glycoside Derivatives on NAFLD in Mice by Modulating the Gut Microbiota and Host Metabolism. J Agric Food Chem 2022;70(46):14732–14743. doi:10.1021/acs.jafc.2c06212, PMID:36351282.
[267] Dong J, Zhang X, Zhang L, Bian HX, Xu N, Bao B, *et al*. Quercetin reduces obesity-associated ATM infiltration and inflammation in mice: a mechanism including AMPKα1/SIRT1. J Lipid Res 2014;55(3):363–374. doi:10.1194/jlr.M038786, PMID:24465016.
[268] Cao P, Wang Y, Zhang C, Sullivan MA, Chen W, Jing X, *et al*. Quercetin ameliorates nonalcoholic fatty liver disease (NAFLD) via the promotion of AMPK-mediated hepatic mitophagy. J Nutr Biochem 2023;120:109414. doi:10.1016/j.jnutbio.2023.109414, PMID:37423322.
[269] Nie T, Wang X, Li A, Shan A, Ma J. The promotion of fatty acid β-oxidation by hesperidin via activating SIRT1/PGC1α to improve NAFLD induced by a high-fat diet. Food Funct 2024;15(1):372–386. doi:10.1039/d3fo04348g, PMID:38099440.
[270] Li X, Yao Y, Wang Y, Hua L, Wu M, Chen F, *et al*. Effect of Hesperidin Supplementation on Liver Metabolomics and Gut Microbiota in a High-Fat Diet-Induced NAFLD Mice Model. J Agric Food Chem 2022;70(36):11224–11235. doi:10.1021/acs.jafc.2c02334, PMID:36048007.
[271] Chen H, Nie T, Zhang P, Ma J, Shan A. Hesperidin attenuates hepatic lipid accumulation in mice fed high-fat diet and oleic acid induced HepG2 via AMPK activation. Life Sci 2022;296:120428. doi:10.1016/j.lfs.2022.120428, PMID:35218767.
[272] Wang SW, Sheng H, Bai YF, Weng YY, Fan XY, Lou LJ, *et al*. Neohesperidin enhances PGC-1α-mediated mitochondrial biogenesis and alleviates hepatic steatosis in high fat diet fed mice. Nutr Diabetes 2020;10(1):27. doi:10.1038/s41387-020-00130-3, PMID:32759940.
[273] Jin HL, Feng XY, Feng SL, Dai L, Zhu WT, Yuan ZW. Isoquercitrin attenuates the progression of non-alcoholic steatohepatitis in mice by modulating galectin-3-mediated insulin resistance and lipid metabolism. Phytomedicine 2024;123:155188. doi:10.1016/j.phymed.2023.155188, PMID:38056146.
[274] Mezhibovsky E, Knowles KA, He Q, Sui K, Tveter KM, Duran RM, *et al*. Grape Polyphenols Attenuate Diet-Induced Obesity and Hepatic Steatosis in Mice in Association With Reduced Butyrate and Increased Markers of Intestinal Carbohydrate Oxidation. Front Nutr 2021;8:675267. doi:10.3389/fnut.2021.675267, PMID:34195217.
[275] Wang D, Zhang M, Zhang Y, Yin Z, Zhang S, Zhao Z, *et al*. Hepatoprotective effects of polysaccharide from Morchella esculenta are associated with activation of the AMPK/Sirt1 signaling pathway in mice with NAFLD. Int J Biol Macromol 2025;301:140444. doi:10.1016/j.ijbiomac.2025.140444, PMID:39884630.
[276] Malladi N, Lahamge D, Somwanshi BS, Tiwari V, Deshmukh K, Balani JK, *et al*. Paricalcitol attenuates oxidative stress and inflammatory response in the liver of NAFLD rats by regulating FOXO3a and NFκB acetylation. Cell Signal 2024;121:111299. doi:10.1016/j.cellsig.2024.111299, PMID:39004324.
[277] Cui X, Yao M, Feng Y, Li C, Li Y, Guo D, *et al*. Exogenous hydrogen sulfide alleviates hepatic endoplasmic reticulum stress via SIRT1/FoxO1/PCSK9 pathway in NAFLD. FASEB J 2023;37(8):e23027. doi:10.1096/fj.202201705RR, PMID:37410029.
[278] Yan BF, Pan LF, Quan YF, Sha Q, Zhang JZ, Zhang YF, *et al*. Huangqin decoction alleviates lipid metabolism disorders and insulin resistance in nonalcoholic fatty liver disease by triggering Sirt1/NF-κB pathway. World J Gastroenterol 2023;29(31):4744–4762. doi:10.3748/wjg.v29.i31.4744, PMID:37664157.
[279] Mitchell SJ, Martin-Montalvo A, Mercken EM, Palacios HH, Ward TM, Abulwerdi G, *et al*. The SIRT1 activator SRT1720 extends lifespan and improves health of mice fed a standard diet. Cell Rep 2014;6(5):836–843. doi:10.1016/j.celrep.2014.01.031, PMID:24582957.
[280] Wu H, Wu J, Zhou S, Huang W, Li Y, Zhang H, *et al*. SRT2104 attenuates diabetes-induced aortic endothelial dysfunction via inhibition of P53. J Endocrinol 2018;237(1):1–14. doi:10.1530/JOE-17-0672, PMID:29371235.
[281] Isaacs-Ten A, Moreno-Gonzalez M, Bone C, Martens A, Bernuzzi F, Ludwig T, *et al*. Metabolic Regulation of Macrophages by SIRT1 Determines Activation During Cholestatic Liver Disease in Mice. Cell Mol Gastroenterol Hepatol 2022;13(4):1019–1039. doi:10.1016/j.jcmgh.2021.12.010, PMID:34952202.