Review

Sirtuins and Gut Microbiota: Dynamics in Health and a Journey from Metabolic Dysfunction to Hepatocellular Carcinoma

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Review

Sirtuins and Gut Microbiota: Dynamics in Health and a Journey from Metabolic Dysfunction to Hepatocellular Carcinoma

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Abstract: Metabolic dysfunction leading to non-alcoholic fatty liver disease (NAFLD) exhibits distinct molecular and immune signatures that are influenced by factors like gut microbiota. The gut microbiome interacts with the liver via a bidirectional relationship with the gut-liver axis. Microbial metabolites, sirtuins and immune responses play a pivotal role in different metabolic diseases. This extensive review explores the complex and multifaceted interrelationship between sirtuins and gut microbiota, highlighting their importance in both health and disease, particularly in relation to metabolic dysfunction and hepatocellular carcinoma (HCC). Sirtuins (SIRTs), classified as a group of NAD+-dependent deacetylases, serve as crucial modulators of a wide spectrum of cellular functions, including metabolic pathways, the inflammatory response, and the process of senescence. Their subcellular localization and diverse functions link them to various health conditions, including NAFLD and cancer. Concurrently, the gut microbiota, comprising diverse microorganisms, significantly influences host metabolism and immune responses. Recent findings indicate that sirtuins modulate gut microbiota composition and function, while the microbiota can affect sirtuin activity. This bidirectional relationship is particularly relevant in metabolic disorders, where dysbiosis contributes to disease progression. The review highlights recent findings on the roles of specific sirtuins in maintaining gut health and their implications in metabolic dysfunction and HCC development. Understanding these interactions offers potential therapeutic avenues for managing diseases linked to metabolic dysregulation and liver pathology.

Keywords: sirtuins (SIRTs); gut microbiota; metabolic dysfunction; hepatocellular carcinoma (HCC); non-alcoholic fatty liver disease (nafld)

1. Background

Sirtuins (SIRTs), categorized as class III histone deacetylases (HDACs), have emerged as a crucial regulators in numerous cellular mechanisms, particularly those related to aging, metabolism, and disease [1,2]. These NAD^+-dependent enzymes serve a crucial function in the preservation of cellular homeostasis by deacetylating histones, transcription factors, and other proteins, thus influencing gene expression and metabolic pathways. Research has increasingly highlighted the significance of sirtuins in health conditions ranging from metabolic dysfunction to cancer, particularly hepatocellular carcinoma (HCC) [3].

The gut microbiota, which harbors an intricate consortium of microorganisms that inhabit the intestinal tract, has also been recognized for its profound impact on host health [4]. Emerging evidence indicates that sirtuins and gut microbiota significantly influence metabolic health and

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disease outcomes [4]. Sirtuins affect gut microbiota by enhancing gut barrier integrity and immune modulation. Conversely, gut microbiota-derived metabolites can impact sirtuin activity, creating a dynamic feedback loop that affects overall health [5].

The intricate dynamics between sirtuins and gut microbiota are pivotal in the study of NAFLD and its development into HCC [3]. As the prevalence of NAFLD increases, it is imperative to elucidate its molecular pathogenesis for the advancement of effective therapeutic strategies [6]. This review explores the correlation between sirtuins and gut microbiota in the context of health and disease, elucidating their roles in metabolic dysfunction and the progression to liver cancer. By integrating insights from recent research, we aim to highlight potential therapeutic interventions targeting these pathways to improve health outcomes. Additionally, we propose future research directions to investigate sirtuin-microbiota interactions, paving the way for innovative strategies in preventing and treating metabolic disorders and liver cancer.

2. Overview of Sirtuins and Their Biological Functions

1.1. Sirtuins Classification and Subcellular Localization

Sirtuins (SIRTs), a group of proteins known as class III HDACs, play a pivotal in various cellular processes and have a significant impact in aging research and related diseases. [1,2]. They catalyse NAD+ dependent deacetylation reaction linking them with the metabolic regulation. Structurally, sirtuins conatin a N-terminal, C-terminal and Zinc binding domain. SIRT1-7 have a structurally conserved catalytic core bearing two bi-lobed globular domains comprising of 275 amino acid residues harbouring NAD^+ as a cofactor. Isoform specific N and C-terminal domains are variable in their length, chemical composition and susceptibility to post-translational modifications (PTM) subsequently regulating its localization and regulation [7].

Phylogenetic analysis based on the amino acid sequence revealed four different classes of sirtuins. SIRT1-3 belong to Class I, SIRT-4 to Class II, SIRT 5 to Class III, SIRT6-7 to Class IV [7]. Each protein exhibits distinct subcellular compartmentalization [8]. SIRT1, 6, and 7 predominantly reside within the nucleus. However, SIRT1 can translocate to the cytoplasm under physiological or pathological stimuli [9]. SIRT2, on the other hand, is primarily situated within the cytoplasm but is capable of translocating to the nucleus under certain conditions to influence cellular processes [10]. Additionally, SIRT3 can also undergo relocation between the mitochondria and the nucleus, enabling it, to regulate a wide range of cellular processes [11]. while SIRT 4, and 5 are typically located in the mitochondrial compartment [7,12]. These dynamic subcellular distributions and trafficking abilities allow the sirtuins to coordinate their regulatory functions across different compartments of the cell [13]. SIRTs play a key regulatory role in metabolism, health-span, and longevity by deacetylating histones, transcriptional regulators, and other proteins, in addition to their ADP-ribosyltransferase and deacytlase activities [2,14].

Table 1. SIRT1, SIRT2, and SIRT3 function as deacetylases, primarily localized in the nucleus, cytoplasm, and mitochondria, respectively. SIRT4 acts as an ADP-ribosyltransferase and is also localized to the mitochondria. SIRT5 possesses both deacetylase and deacylase activities within the mitochondrial compartment. SIRT6 operates as both a deacetylase and an ADP-ribosyltransferase, predominantly found in the nucleolus, while SIRT7 is identified as a nuclear deacetylase.

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	Location	Enzymatic Activity
SIRT1	Nucleus, Cytoplasm	Deacetylase
SIRT2	Cytoplasm, Nucleus	Deacetylase
SIRT3	Mitochondria, Cytoplasm	Deacetylase
SIRT4	Mitochondria	ADP-ribosyltransferase
SIRT5	Mitochondria	Deacetylase, Deacylase
SIRT6	Nucleus	Deacetylase, ADP-ribosyltransferase
SIRT7	Nucleolus	Deacetylase

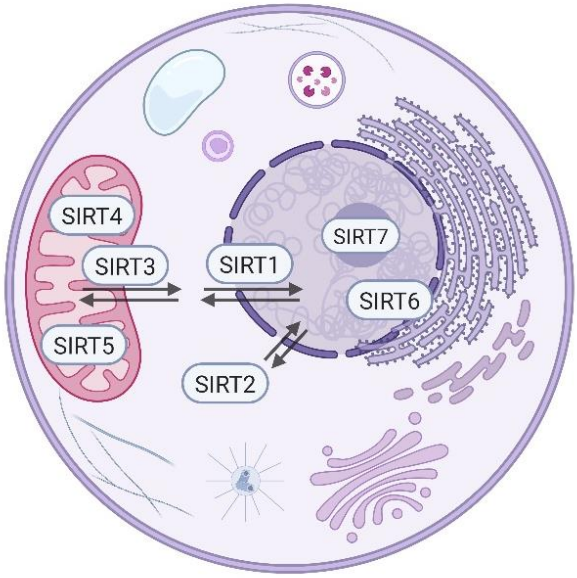

Figure 1. Subcellular Localizations and Catalytic Functions of Human Sirtuins.

1.2. Role of Sirtuins in Cellular Homeostasis and Metabolism

SIRTs are involved in post-translational modifications, particularly protein deacetylation, and contribute to gene expression regulation, DNA repair, and cellular senescence [15]. These enzymes enhance genomic stability through chromatin structural modulation and involvement in various DNA repair mechanisms, including base excision repair, nucleotide excision repair, and double-strand break repair [16,17]. SIRTs also serve a crucial role in the modification of histones and proteins, influencing cellular metabolism, mitochondrial function, and stem cell maintenance [18,19]. SIRT1, the most widely studied sirtuin, is recognized for its role in transcriptional regulation, genomic silencing, and epigenetic elements within the nucleus, while also contributing to metabolism and nutrient perception in the cytosol [20]. The involvement of SIRTs in aging and cancer has been extensively studied, with different sirtuin family members showing diverse effects on stem cells and cancer cells [21,22].

SIRTs play vital roles in various physiological and pathological conditions, such as neurodegenerative diseases [23], kidney disorders [24], and cardiovascular diseases [8]. They are important for maintaining cellular integrity [25] and regulating metabolic balance, including glucose and lipid metabolism [26]. Additionally, they modulate mitochondrial activity and have been associated with various metabolic disorders [8]. SIRTs also contribute to the regulation of female reproductive processes [27] and influence women's health, particularly in ovarian function and cancer development [28]. In the immune system, SIRTs modulate T cell metabolism and function, making them promising therapeutic targets for immune-related diseases [29]. Furthermore, SIRTs have been implicated in counteracting several hallmarks of aging, potentially contributing to healthy longevity [30].

Different investigations underscore the crucial and multifaceted functions of sirtuins in neoplastic advancement, acting as tumor suppressors as well as activators of tumorigenesis, depending on the specific cellular environment.[31,32]. SIRTs regulate various cancer-related processes, including cell viability, apoptosis, metastasis, and metabolism [31,33]. Among all SIRTs, SIRT1 has been extensively researched for its dual role in cancer, contributing to tumor suppression and promotion [34,35]. SIRT2's role remains controversial, with evidence suggesting it can act as either an oncogene or a tumor suppressor across multiple malignancies [36]. The roles of other sirtuins (SIRT3-7) vary across different cancer types, influencing processes such as proliferation, invasion, and chemoresistance [37–39]. Furthermore, SIRTs play crucial roles in hepatocellular carcinoma (HCC) development and progression [3,40]. SIRT1 is overexpressed in HCC, promoting

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oncogenesis and multidrug resistance [41]. Collectively, these findings emphasize sirtuins' vital role in cellular homeostasis and disease management, particularly in cancer, necessitating further investigation into their specific functions and therapeutic implications.

Table 1. Classification and Functional Roles of Sirtuins in Metabolism and Cellular Processes.

Sirtuin	Class	Type of Activity	Acyl Substrates	Cellular Function	Target substrates	Metabolic role	Biological role
SIRT1	I	Strong deacytylase activity	Remove acetyl and long chain fatty acyl group from Lysine	Formation of facultative chromatin, Mitochondrial biogenesis,	p53, FOXO1/3, NF-κB, CRTC2, PGAM-1, PGC1α, SREBP, LXR, FXR, LKB1	Fatty acid oxidation, Regulation of cholesterol and bile acid homeostasis	Cell survival and lipid metabolism
SIRT2	I	Both deacetylase and mono-ADP-ribosyl transferase activity	Remove of acetyl, long-chain fatty acyl, 4-oxononanoyl, and benzoyl groups	Cell cycle regulation, Tumor suppression /promotion Neurodegeneration	α-Tubulin, FOXO1, FOXO3, p300	Promotion of lipolysis in adipocytes	Regulation of cell cycle and cell motility
SIRT3	I	Both deacetylase and mono-ADP-ribosyl transferase activity	Remove acetyl and long-chain fatty acyl groups from lysine	Regulation of mitochondrial activity Protection against oxidative stress Tumor suppression	LCAD, ACS2, SOD2, IDH2, HMGCS, OTC, SOD2, subunits of the electron transport chain and ATP synthase		Metabolism and thermogenesis
SIRT4	Class II	Mono-ADP-ribosyl	Remove	Tumor suppression	IDE, ANT2,	Glucose metabolism	Glucose

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		transferase activity	lipoyl, biotinyl, methylglutaryl, hydroxymethylglutaryl, and 3-methylglutaconyl groups		ANT3, GDH, MCD, PDH	Amino acid catabolism	metabolism and Insulin secretion
SIRT5	Class III	Weak deacetylase activity	Removes charged malonyl, succinyl, and glutaryl groups		CPS1, UOX	Urea cycle Fatty acid metabolism Amino acid metabolism	Cellular energy Metabolism
SIRT6	Class IV	Mono-ADP-ribosyl transferase activity	Remove acetyl and long-chain fatty acyl groups	Genomic stability/DNA repair	HIF1α, PARP1, TNFα, GCN5	Glucose and lipid metabolism Inflammation	DNA repair/Glucose homeostasis
SIRT7	Class IV	Mono-ADP-ribosyl transferase activity	Remove acetyl groups	Ribosome biogenesis Tumor promotion	RNA polymerase 1		Metabolism, rDNA transcription

3. The Role of Gut Microbiota in Host Health and Disease

The gut microbiota includes a variety of microorganisms, such as bacteria, archaea, fungi, viruses, and parasites [42–44]. These microorganisms, inhabit within the gastrointestinal tract—particularly in the intestinal—are commonly designated as gut flora or gut microbiota [45]. While bacteria dominate the gut microbiome, the significance of other microbes—often referred to as the "dark matter" of microbiomes—has become increasingly recognized [43]. The predominant bacterial phyla present within the human gut microbiome include Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria [46]. Furthermore, this complex community plays essential roles in host physiology, metabolism, and immune function [47,48]. The gut microbiota helps maintain intestinal integrity through the production of microbial metabolites and anti-microbial peptides modulating the immunity [49]. Additionally, it serves as a potential source of novel antimicrobials, which could help address antimicrobial resistance [50]. Moreover, the gut microbiota contributes significantly to digestion by breaking down indigestible dietary components and producing essential nutrients like vitamins and enzymes [51]. Furthermore, the microbiota plays a critical role in

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modulating inflammation, cancer-related processes, and oxidative stress through the production of metabolites, especially short-chain fatty acids (SCFAs) and tryptophan catabolites [52–55].

Gut microbiota are essential for the fermentation of non-digestible carbohydrates, yielding SCFAs such as acetate, propionate, and butyrate [56,57]. These SCFAs serve as energy sources for colonocytes and maintain gut barrier integrity [58,59]. Moreover, SCFAs influence host metabolic processes and immune responses via diverse mechanisms, such as the stimulation of G-protein-coupled receptors and the suppression of histone deacetylases [60]. The gut microbiota is also participates in bile acid metabolism, which is essential for lipid digestion and absorption [61]. Consequently, microbial SCFA production and bile acid metabolism significantly impact host health via intricate interactions with the gut epithelium, immune response, and metabolic pathways [62,63]. Grasping these mechanisms is essential for developing approaches to enhance gut health and avoid metabolic diseases.

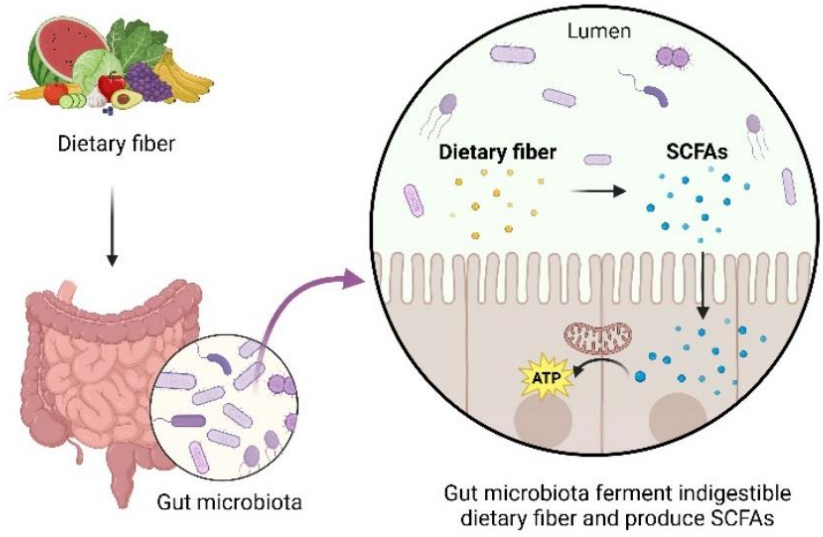

Figure 2. The Role of Gut Microbiota in SCFAs Production and Metabolic Health.

Gut microbiota produce SCFAs via the fermentation of indigestible carbohydrates. These organic acids, typically containing fewer than six carbon atoms, play essential roles in energy metabolism and the synthesis of vital molecules, significantly contributing to energy homeostasis and overall metabolic health.

The composition of gut microbiota is modulated by factors including diet, genetics, and environmental conditions [64–66]. Diet significantly influences the microbiome, alongside seasonal and geographical factors impacting dietary habits and microbial composition [67]. Environmental determinants, such as communal residences, exert a more significant influence on microbiome composition than host genetics [68]. Nevertheless, host genetics continue to exert an influence in ascertaining microbiome composition, especially via immune system-related genes [69]. Early life factors, including birth mode, feeding methods, and antibiotic use, also contribute to microbiota development [70]. The gut microbiome is dynamic, changing throughout an individual's lifetime due to factors like age, BMI, exercise, and lifestyle [66]. Recognizing these influences is important for maintaining a healthy microbiome and preventing dysbiosis, which has been linked to several diseases [65,71].

Dysbiosis, characterized by a perturbation in the assemblage of gastrointestinal microbiota, has been associated with numerous pathological states, encompassing inflammatory bowel disease (IBD), cardiovascular diseases, diabetes mellitus, obesity, and various neurological disorders [72–76]. This dysbiosis frequently presents as a diminution in microbial variety alongside an elevation in particular bacterial taxa [75]. Factors contributing to dysbiosis include antibiotic use, diet, and environmental

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stressors [74,75]. Dysbiosis can lead to altered microbial metabolite production, immune dysregulation, and chronic inflammation [77]. Therapeutic modalities aimed at addressing dysbiosis encompass fecal microbiota transplantation, the administration of probiotics, the utilization of prebiotics, as well as various dietary interventions [78,79].

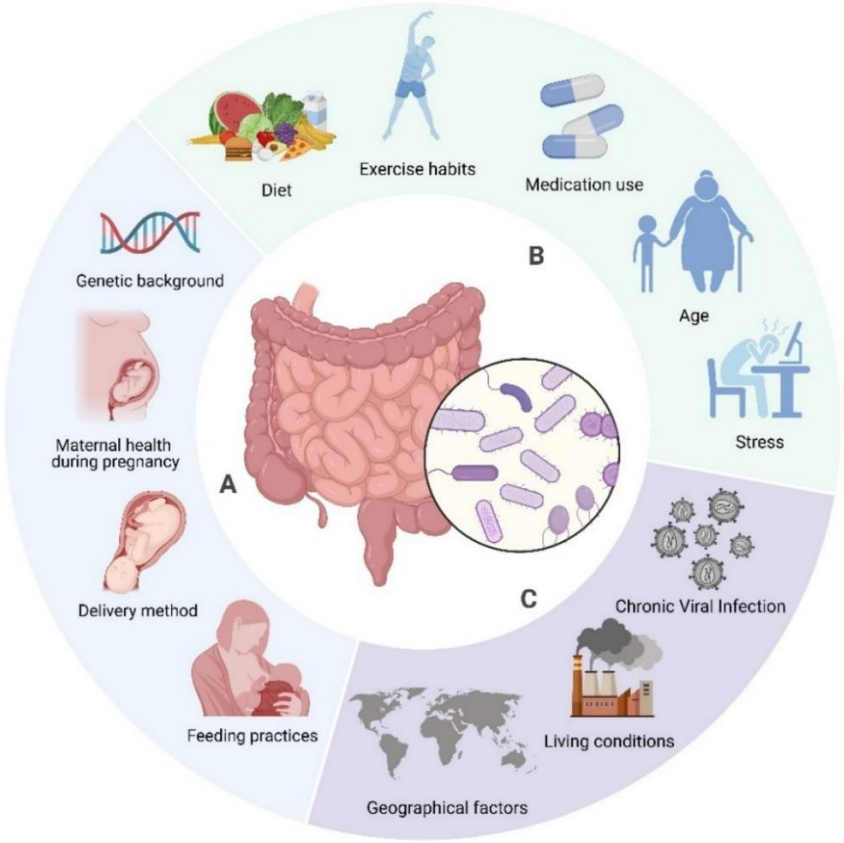

Figure 3. Determinants of Gut Microbiome Composition.

The gut microbiota composition is affected by a wide range of factors. Some elements, such as genetic background, delivery method, early infant feeding practices, and maternal health during pregnancy, are established early in life and tend to remain stable (A). In contrast, factors like diet, medication use, exercise habits, age, and stress levels are more variable and can be modified throughout life (B). Furthermore, environmental influences, including chronic viral infections, living conditions, and geographical factors, also contribute to microbiome composition, although these may be more challenging to alter (C).

4. Interrelationship Between Sirtuins and Gut Microbiota: A Bidirectional Perspective

4.1. Influence of Sirtuins on Gut Microbiota Composition

Sirtuins are essential in gut function regulation, particularly in preserving the intestinal barrier and mucosal immune mechanism, which are vital for regulating intestinal microbiota composition [80].

SIRT1

Intestinal epithelial SIRT1 regulates gut microbial composition consequently preventing age related intestinal inflammation[81]. The gut microbiome remotely regulates the expression of miR-204 subsequently impairing the endothelial function by targeting Sirt1[82]. SIRT1 deficiency in the intestinal epithelium leads to increased fecal bile acid levels, reduced *Lactobacillus* abundance, and heightened susceptibility to intestinal inflammation and colitis [83]. Moreover, the gut microbiome

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modulates systemic hydrogen sulphide levels impacting SIRT1 activation followed by regulation of neurinflammation [84].

SIRT2

Similarly, SIRT2 deficiency enhances the progression of NAFLD by altering gut microbiota composition and inducing metabolic disorders [6]. whereas inhibiting SIRT2 may improve gut barrier integrity and protect against colitis [85]. SIRT2 knockout mouse displayed increased susceptibility to obesity, liver injury and metabolic dysfunction when placed on high fat/high sucrose/high cholesterol diet [6].

SIRT3

SIRT3 and the gut microbiota interaction leads to modulation of key cellular processes like mitochondrial function, inflammation and energy metabolism[86]. SIRT3 deficiency promotes NAFLD progression through gut microbial dysbiosis and impaired intestinal permeability [87]. Moreover, the gut microbiota modulates hydrogen sulphide levels consequently affecting SIRT3 activation [84].

SIRT4

Mitochondrial SIRT4 regulates intestinal metabolism and homeostasis. It regulates lysozyme expression in the gut, influencing microbiota composition [88]. Loss of SIRT4 can lead to dysregulated glutamine and nucleotide metabolism in intestinal adenomas [89].

SIRT5 -7

While the roles of SIRT5, SIRT6, and SIRT7 in gut microbiota regulation are not directly established, it is notable that downregulation of SIRT5 has been linked to increased bile acid production, which may contribute to an immunosuppressive tumor microenvironment and facilitate hepatocellular carcinoma (HCC) development [90]. Moreover, SIRT6 knockout mice exhibit premature aging associated with gut dysbiosis, a condition reversible through fecal microbiota transplantation or a high-fat diet [91]. It is noteworthy that the presence of an inflammatory response of the colorectal mucosa is associated with higher concentrations of SIRT7 and lower concentrations of SIRT1 [92].

Together, these roles underscore the importance of sirtuins in gut health and their potential influence on microbiota dynamics, highlighting areas for future research.

Table 2. Roles of Sirtuins in Gut Health: Impact on Barrier Integrity, Inflammation, and Microbial Diversity.

Sirtuin	*Roles of Sirtuins in Gut Health*	*Ref.*
SIRT1	Maintains intestinal epithelial barrier integrity, regulates inflammation, and modulates autophagy, potentially influencing gut microbiota composition and diversity.	[81,93–95]
SIRT2	Regulates intestinal epithelial cell proliferation and differentiation, impacting the gut environment and reducing inflammation, facilitating better host-microbiota interactions.	[85,96,97]
SIRT3	Enhances mitochondrial function in intestinal cells, regulates oxidative stress, and maintains gut barrier homeostasis; deficiency leads to microbial dysbiosis and impaired permeability.	[84,98,99]
SIRT4	Modulates amino acid metabolism in intestinal cells, potentially influencing nutrient availability for gut microbiota.	[89,100]
SIRT5	Regulates cellular homeostasis and various metabolic pathways in intestinal cells, potentially influencing nutrient availability for gut microbiota.	[101,102]

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SIRT6	Maintains intestinal epithelial barrier integrity, mitigates inflammation, and enhances favourable immune responses; may affect gut microbiota composition and diversity.	[103–105]
SIRT7	Maintains intestinal homeostasis and modulates inflammation; potentially affecting gut microbiota composition.	[92,106]

4.2. Impact of Gut Microbiota on Sirtuin Activity

Conversely, gut microbiota also influences sirtuin activity and expression. Studies indicate that gut microbiota can regulate the expression of sirtuins, along with senescence-regulating miRNAs and mitochondrial DNA, all associated with overall well-being [107]. Moreover, gut microbiota interacts with sirtuin-activating compounds to influence molecular pathways that counteract aging and inflammation, while enhancing specific gut microbiota groups to improve immune function [108].

Studies have elucidated that gastrointestinal microbiota may influence critical transcriptional co-activators, transcription factors, and enzymatic pathways pertinent to mitochondrial biogenesis, encompassing genes such as PGC-1α, SIRT1, and AMPK [109]. Additionally, the gut microbiome regulates vascular microRNA-204, which targets SIRT1 and affects endothelial function [82]. Furthermore, metabolites produced by gut microbiota from fermenting indigestible food components can impact sirtuin function [110]. For instance, gut microbiota-derived metabolites have anti-inflammatory and antioxidative properties that influence sirtuin activity [111]. Particularly, Urolithin A (UroA), a microbial metabolite derived from polyphenolics, exemplifies this by exhibiting anti-inflammatory and antioxidative effects [111]. These properties of microbial metabolites can directly affect sirtuin function, as sirtuins are involved in regulating oxidative stress and inflammation [112]. By modulating these pathways, gut microbiota-derived metabolites can indirectly affect sirtuin activity and contribute to overall host health.

Additionally, the gut microbiome possesses the capacity to affect sirtuin-associated pathways; for example, *Saccharomyces boulardii* has been demonstrated to alter necrotizing enterocolitis through the modulation of the SIRT1/NF-κB signaling pathway and the intestinal microbiota [113]. The overall outcomes shed light on the intricate relationship between sirtuins and gut microbiota, stressing the requirement for more extensive investigation to clarify current shortcomings in understanding their roles and interconnections.

5. Role of Sirtuins and Gut Microbiota in Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD represents the most widespread form of chronic hepatic disorder globally and is projected to emerge as the primary etiology for liver transplantation by the year 2030 [114]. Furthermore, NAFLD is distinguished by an atypical aggregation of hepatic lipids., concomitant with insulin resistance, and demonstrable steatosis, while systematically ruling out secondary etiologies of hepatic steatosis, such as alcohol consumption [115]. Additionally, NAFLD comprises a spectrum of disorders extending from hepatic steatosis to steatohepatitis, leading to inflammation, hepatocirrhosis, hepatocellular carcinoma, and mortality [116]. Also, is closely associated with insulin resistance and may function as both a cause and a result of metabolic syndrome [117].

Formerly, the "two-hit" hypothesis previously explained NAFLD pathogenesis, identifying lipid accumulation as the "first hit." This initial accumulation of lipid predisposes the liver to further injury, termed the "second hit," resulting in inflammation and fibrosis [118]. Recent research proposes the multiple-hit hypothesis, which more comprehensively describes the molecular and metabolic alterations in NAFLD. This updated framework includes interconnected mechanisms such as insulin resistance, lipotoxicity, innate immune activation, and gut microbiome effects, influenced by genetic (PNPLA3) and dietary elements (saturated fat and fructose) [118].

The interplay between sirtuins and intestinal microbiota is a complex relationship. The gut microbiota plays a crucial role in host metabolism by breaking down nutrients and producing

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metabolites that influence metabolic processes and modulate immunity [119]. Sirtuins are recognized for their ability to govern the intestinal microbiome, thereby suggesting their participation in the pathophysiological mechanisms underlying a variety of diseases. They are integral to numerous physiological processes, encompassing glucose and lipid metabolism, insulin resistance, and mitochondrial function, thereby rendering them pivotal factors in the etiology of conditions such as type 2 diabetes, obesity, and NAFLD [120–122]. Furthermore, sirtuins influence essential metabolic hormones such as leptin, ghrelin, melatonin, and serotonin, which perform a crucial function in the regulation of gastrointestinal homeostasis [123].

Recent studies indicate a significant reduction of sirtuin levels in NAFLD patients. Wu et al. found decreased expression of SIRT1, SIRT3, SIRT5, and SIRT6 in NAFLD patients, alongside increased lipogenic gene expression and SIRT4 [124]. Furthermore, Bruce et al. demonstrated that excess dietary fat exposure during early and postnatal periods elevates NASH risk in adulthood, particularly affecting sirtuin levels. Offspring on a high-fat diet exhibited NAFLD, with those from high-fat diet mothers developing NASH, characterized by decreased NAD+/NADH and lower SIRT1 and SIRT3 levels, coupled with increased lipid metabolism gene expression [125].

The gut microbiota is essential for NAFLD development through dietary metabolism, yielding vital nutrients and energy [126–128]. Its composition is diet-dependent, with high-fat/high-cholesterol (HFC) and high-fat/high-sucrose (HFS) diets causing dysbiosis linked to NAFLD [129–131]. This dysbiosis increases intestinal permeability, exposing the liver to bacterial products through the portal vein and inducing metabolic endotoxemia, thereby disrupting the gut-liver axis [132,133]. NAFLD microbiota differs from that of healthy individuals and is influenced by genetic factors related to metabolic syndrome [134,135]. Additionally, gastrointestinal microbiomes can synthesize lipopolysaccharides (LPS), which may infiltrate the circulatory system and impair the hepatic tissue when the intestinal barrier is compromised (Figure 4) [131,136]. In contrast, SCFAs such as butyrate are crucial for maintaining gut barrier integrity. Zhou et al. demonstrated that sodium butyrate enhances gut microbiota and fortifies the intestinal barrier, mitigating LPS translocation and reducing steatohepatitis in mice [137]. This underscores the significance of a robust gut barrier.

Chen et al. demonstrated that SIRT3 deficiency worsens NAFLD from a high-fat diet through impaired intestinal permeability linked to gut microbial dysbiosis in SIRT3 knockout mice. The SIRT3KO mice exhibited increased Oscillibacter, Parabacteroides, and Mucispirillum, while Alloprevotella decreased [98]. Prior studies have shown a negative correlation between Oscillibacter levels and the mRNA expression of zonula occludens-1, a protein relevant to gut permeability [138–140]. Furthermore, Everard et al. noted increased Mucispirillum and Parabacteroides in humans and mice on a high-fat diet [141]. The elevation of Oscillibacter, Mucispirillum, and Parabacteroides correlates with exacerbated HFD-induced NAFLD in SIRT3KO mice, characterized by diminished tight junction protein expression like ZO-1 and claudins [98]. Thus, SIRT3-mediated intestinal barrier dysfunction, coupled with LPS release from gut microbiome alterations, facilitates NAFLD progression.

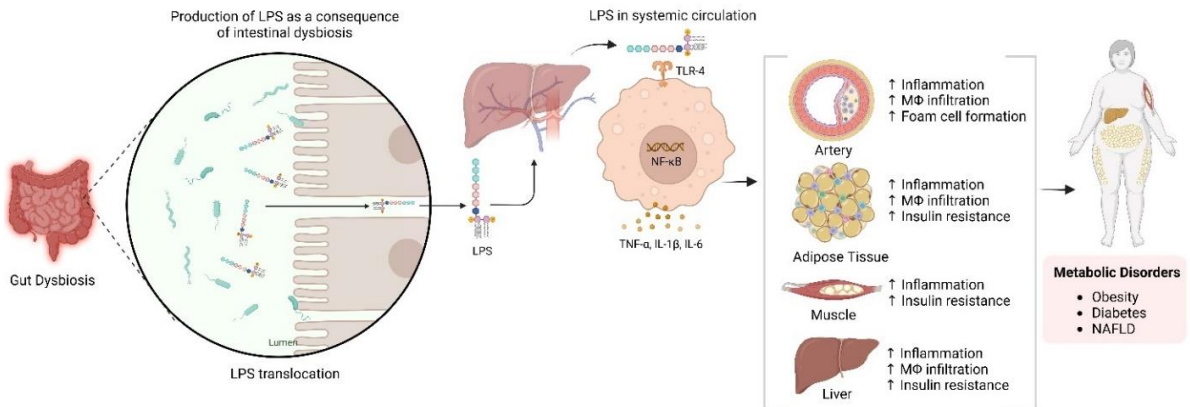

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Figure 4. Impact of Gut Dysbiosis on Inflammation and Metabolic Dysfunction.

This figure depicts events following gut dysbiosis, leading to LPS release. These LPS molecules reach the liver via the portal vein, activating macrophages through Toll-like receptor 4 (TLR4). This activation induces proinflammatory cytokine release, including TNFα, IL-1β, and IL-6, resulting in heightened inflammation and hepatic insulin resistance. Additionally, activated macrophages infiltrate adipose tissue, worsening inflammation and insulin resistance, thereby contributing to metabolic disorders, including obesity, diabetes, and NAFLD.

6. Role of Sirtuins and Gut Microbiota in Hepatocellular Carcinoma (HCC)

Liver cancer represents a considerable global health issue, with rising rates primarily attributed to hepatocellular carcinoma (HCC), which constitutes about 90% of cases [142,143]. Significant risk factors for HCC development include chronic hepatitis B and C virus infections. Non-viral factors involve environmental carcinogens such as aflatoxin B1, alcohol misuse, and genetic conditions like hemochromatosis and Wilson disease [144]. Importantly, non-alcoholic steatohepatitis (NASH) has emerged as a critical criterion for liver transplantation among HCC patients in the United States [145]. The transition from NAFLD to HCC entails a multifaceted interaction of metabolic variables, inflammation, gut microbiota imbalance, oxidative stress, and aberrant lipid metabolism [146–148]. Dysbiosis, has been implicated in the pathogenesis of HCC and its related chronic diseases, which encompass chronic hepatitis B and C, alcoholic liver disease, NAFLD, and NASH [149].

SIRT1 has a critical role in HCC by virtue of promoting tumorigenicity, metastasis, chemoresistance, and heralding a poor prognosis [150–152]. The interplay between SIRT1 and intestinal microbiota is complex. Butyrate, a short-chain fatty acid from gut bacteria, is crucial in this relationship. A decrease in butyrate-producing bacteria may harm the intestinal mucosa, possibly leading to HCC development [153]. Pant et al. illustrated that butyrate induces microRNA-22 (miR-22), which downregulates SIRT1 in a concentration-dependent manner, increasing reactive oxygen species (ROS) and apoptosis in hepatic cells exposed to sodium butyrate [154]. MiR-22's downregulation in human liver cancer cells correlates with enhanced tumorigenicity and cellular proliferation [155]. It is implicated in HCC development via the miR-29a-SIRT1-WNT/β-catenin pathway [156]. Moreover, overexpression of SIRT1 promotes HCC proliferation and resistance to chemotherapy by promoting autophagy [157,158]. SIRT1 protects mitochondrial function of HCC cells by suppressing the expression of hypoxia-induced factor-1 alpha expression and also promotes stem-cell like features in HCC cells[159]. SIRT1 also promotes HCC metastasis by enhancing PGC-1α-mediated mitochondrial biogenesis[160]. Conversely, Herranz et al. reported that SIRT1 overexpression can protect transgenic animals from diethylnitrosamine/high-fat diet-induced liver cancer by mitigating NF-kB-mediated inflammation and averting malignant transformation [161]. This observation contrasts with earlier assertions of SIRT1's role in promoting HCC and other studies indicating elevated SIRT1 in human HCC samples [162,163]. Malignant cells may utilize survival strategies typically reserved for non-malignant cells [164]. Portmann et al. have demonstrated that inhibiting SIRT1 leads to impaired tumor growth both in vivo and in vitro and this supports that notion that SIRT1 activity in healthy hepatocytes protects against cancer, but after transformation, SIRT1 becomes a protective force for the tumor cells as a survival advantage[165]. However, additional research is essential to elucidate the intricate relationship between butyrate and SIRT1 in the etiology of HCC.

SIRT2 mediates the deacetylation and activation of protein kinase B, impacting the glycogen synthase kinase-3β/β-catenin signaling pathway, which is implicated in epithelial-mesenchymal transition (EMT) [166]. Huang et al. support the tumor-promoting role of SIRT2, revealing that its downregulation hinders energy metabolism and invasion in HCC cells [167]. Further investigation is warranted to elucidate SIRT2's specific functions in HCC.

SIRT7 plays a multifaceted role in HCC, with its upregulation noted in numerous patients [168]. It facilitates HCC cell proliferation through ERK1/2 phosphorylation and activation of the

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RAF/MEK/ERK signaling cascade, promoting tumor growth [169]. Moreover, SIRT7 boosts HCC cell proliferation by inhibiting MST1 and modulating the Hippo/YAP pathway, resulting in enhanced YAP activation [170].

In summary, the interplay between sirtuins and gut microbiota is essential for elucidating the pathogenesis of NAFLD and HCC. Table (3) highlights the microbial changes linked to these diseases, indicating opportunities for specific therapeutic interventions. Subsequent investigations should aim to utilize these findings for the formulation of microbiota-targeted therapies to improve disease management and patient prognosis.

Table 3. Microbiota Composition Changes in NAFLD and HCC: A Summary of Human Studies.

Disease	*Composition Change*		*References*
	Increase	Decrease	
NAFLD	*Streptococcus, Megasphaera, Enterobacteriaceae, Streptococcus, Gallibacterium*	*Bacillus and Lactococcus, Pseudomonas, Faecalibacterium prausnitzii, Catenibacterium, Rikenellaceae, Mogibacterium, Peptostreptococcaceae*	[171]
	Firmicutes (Streptococcus mitis and Roseburia inulinivorans) and Bacteroidetes (Barnesiella intestinihominis and Bacteroides uniformis)	*Bacteroidetes (Prevotella sp.CAG 520, Prevotella sp. AM42 24, Butyricimonas virosa, and Odoribacter splanchnicus), Proteobacteria (Escherichia coli), Lentisphaerae (Victivallis vadensis), and Firmicutes (Holdemanella biformis, Dorea longicatena, Allisonella histaminiformans, and Blautia obeum)*	[172]
	Bacteroidetes, Proteobacteria, Bacteroides, Alistipes, Verrucomicrobia, Faecalibaculum, Helicobacter, Epsilonbacteraeota	*Muribaculaceae, Lactobacillus*	[173]
HCC	*Escherichia coli*		[174]
	Proteobacteria, Desulfococcus, Enterobacter, Prevotella, Veillonella	*Cetobacterium*	[175]
	Bacteroides	*Akkermansia, Bifidobacterium*	[176]
	Neisseria, Enterobacteriaceae, Veillonella, Limnobacter	*Enterococcus, Phyllobacterium, lostridium, Ruminococcus, Coprococcus*	[177]
	Proteobacteria, Enterobacteriaceae, Bacteroides xylanisolvens, B. caecimuris, Ruminococcus gnavus,	*Erysipelotrichaceae, Oscillospiraceae*	[178]

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Clostridium bolteae, Veillonella parvula		
Klebsiella, Haemophilus	*Alistipes, Phascolarctobacterium, Ruminococcus*	[179]

7. Interventions Targeting Sirtuins and Gut Microbiota

SIRTs are pivotal in linking health and disease, highlighting their potential for targeting interventions [180]. The healthcare sector increasingly recognizes the therapeutic value of manipulating the sirtuin pathway and gut microbiome in disease management [181]. SIRT1 and SIRT2, have been identified as potential targets for therapeutic interventions in various gut dysbiosis-mediated diseases, including cancer, neurodegenerative diseases, and metabolic disorders [182,183]. Studies have been limited in demonstrating the pharmacological utility of modifying other sirtuins in the context of disease where gut dysbiosis contributes to the underlying mechanisms.

a. Sirtuin Activators

Resveratrol

One prominent example of therapeutic intervention is the targeted activation of the SIRT1 pathway [184]. Resveratrol, a polyphenolic compound, has demonstrated efficacy in mitigating the progression of NAFLD in both preclinical and clinical contexts [185]. Resveratrol enhances gut microbiota by promoting the proliferation of beneficial bacteria, thereby improving gut health. This effect is characterized by a decrease in harmful bacteria and an increase in short-chain fatty acid (SCFA)-producing bacteria, which contributes to overall gut microbiota balance and metabolic health [186]. Furthermore, resveratrol alleviates NAFLD by strengthening gut barrier integrity, reducing inflammation, and increasing the production of short-chain fatty acids (SCFAs) [187,188]. Additionally, it exhibits potential protective effects against hepatocellular carcinoma through the modulation of inflammatory, angiogenic, and oxidative stress pathways [189]. Resveratrol's proposed mechanism of action involves the modulation of hepatic lipid metabolism and the reduction of oxidative stress, primarily through the activation of the AMPKα/SIRT1 signalling pathway. This activation effectively suppresses the nuclear factor kappa B (NF-κB) inflammatory pathway, resulting in decreased inflammation and reduced hepatic steatosis [190,191]. Figure 5.

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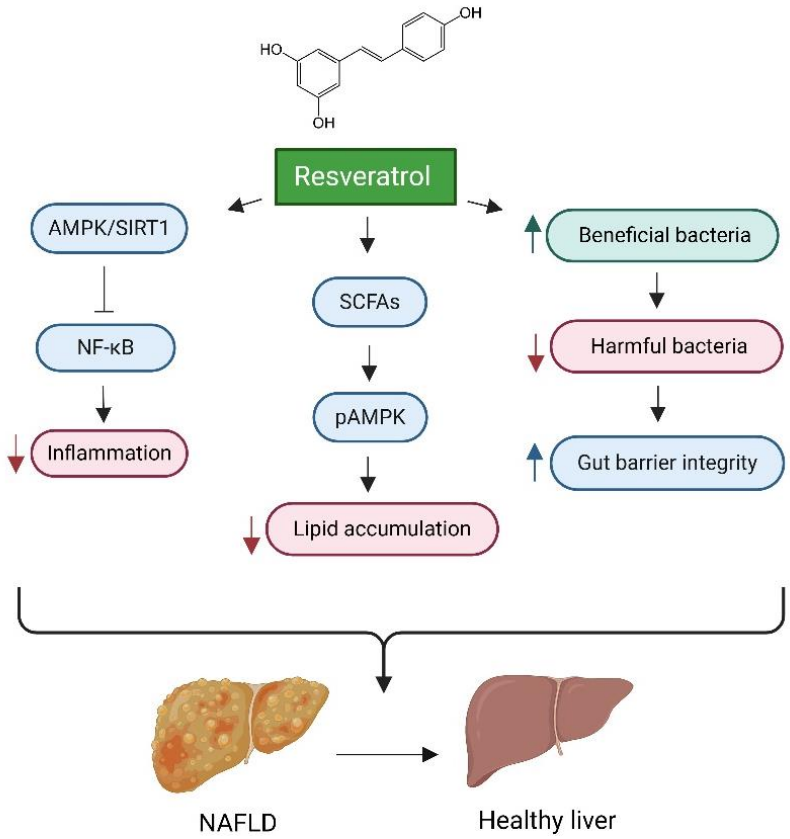

Figure 5. Impact of Resveratrol on Gut Health and Liver Disease.

This figure illustrates the multifaceted mechanisms through which resveratrol mitigates the progression of non-alcoholic fatty liver disease (NAFLD) and improves liver health. Key processes include the enhancement of gut microbiota by promoting beneficial bacterial proliferation, which strengthens gut barrier integrity and overall gut health. Additionally, resveratrol activates the AMPKα/SIRT1 signaling pathway, suppressing the NF-κB inflammatory pathway and leading to decreased inflammation and hepatic steatosis. Furthermore, resveratrol influences hepatic lipid metabolism and reduces lipid accumulation by increasing the production of short-chain fatty acids (SCFAs), which enhances AMPK activation and contributes to decreased lipid accumulation.

Pterostilbene

Pterostilbene, a dimethyl ether variant of resveratrol, exhibits encouraging effects against NAFLD and obesity. It diminishes liver fat accumulation by influencing the miR-34a/Sirt1/SREBP-1 pathway in rats fed a fructose diet [192]. Compared to resveratrol, pterostilbene has enhanced bioavailability and metabolic stability[193]. In rats consuming a high-calorie diet, pterostilbene lowers adipose tissue volume, inhibits lipogenesis in fat tissue, and promotes fatty acid oxidation in the liver [194].From a metabolic perspective, pterostilbene displays greater stability than resveratrol and often shows more potent pharmacological effects [195]. Taken together, these studies indicate that pterostilbene is a promising candidate for addressing NAFLD and obesity, with potential benefits over resveratrol due to its superior bioavailability and metabolic characteristics.

E1231

E1231, treatment activates SIRT1alleviating NAFLD by regulating lipid metabolism. Moreover, E1231 prevented lipid accumulation and improved mitochondrial function in free fatty acid challenged hepatocytes. E1231 prevented liver injury via regulation of SIRT1 and AMPK-α pathway [196].

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Quercetin

Quercetin, a natural flavonoid present in plants, has demonstrated encouraging effects in the treatment of NAFLD. Laboratory studies indicate that quercetin diminishes lipid buildup, lowers inflammatory cytokines, and boosts antioxidant activity in liver cells [197]. Animal studies show that quercetin helps improve NAFLD by triggering AMPK-mediated mitophagy, reducing lipid storage, and alleviating oxidative stress [198] Supplementing the diet with quercetin in gerbils suffering from high-fat diet-induced NASH led to better lipid profiles, a decline in inflammatory markers, and regulation of Sirt1 and NF-κB p65 expression[199]. Thus, the hepatoprotective properties of quercetin are linked to enhanced fatty acid metabolism, anti-inflammatory and antioxidant effects, and modulation of gut microbiota as well as bile acids [200].These results emphasize the potential of quercetin as a therapeutic option for NAFLD.

Nicotinamide Riboside (NR)

Nicotinamide riboside (NR), an NAD+ precursor, shows promise in addressing NAFLD and its progression to HCC. NR supplementation reduces hepatic lipid accumulation, inflammation, and fibrosis in various NAFLD models [201–203]. It activates SIRT1/AMPK-mediated browning of white adipose tissue and modulates gut microbiota, potentially improving lipid metabolism [204].

Berberine

Berberine, a natural plant alkaloid, has emerged as a promising therapeutic agent for NAFLD and its progression to HCC [205]. It exerts beneficial effects on gut microbiota by promoting the growth of beneficial bacterial populations while reducing pathogenic strains [206,207]. Additionally, berberine enhances lipid metabolism, improves insulin sensitivity, and diminishes inflammation [205,208]. Berberine has beneficial effects on NAFLD through various molecular pathways, including the activation of SIRT3, SIRT1, AMPK, and PPAR-γ, as well as the suppression of the NLRP3 pathway [208]. Additionally, berberine activates intestinal farnesoid X receptor (FXR), resulting in increased expression of fibroblast growth factor 15 (FGF15), which in turn inhibits lipogenesis and the activation of NF-κB pathway in the liver [207]. Furthermore, berberine suppresses the p38 MAPK/ERK-COX2 signaling pathways, thereby reducing inflammation and angiogenesis associated with non-alcoholic steatohepatitis (NASH) and HCC [209].

Yinchen Linggui Zhugan Decoction (YLZD)

Yinchen Linggui Zhugan decoction (YLZD), a traditional Chinese medicine, has demonstrated promise in treating NAFLD by modulating the SIRT1/Nrf2 pathway and gut microbiota. In rat models, YLZD treatment has been shown to reduce NAFLD induced by a high-fat diet, increasing serum and fecal butyric acid levels and total SCFAs, while promoting a favorable shift in gut microbiota composition towards SCFA-producing bacteria [210].

The Tangshen Formula (TSF)

The Tangshen formula (TSF), an herbal medicine from China, has exhibited encouraging effects in the management of NAFLD. Research indicates that TSF reduces hepatic steatosis and enhances lipid metabolism in several animal models[211–213]). Its mechanism of action involves various pathways, such as the modulation of gut microbiota and metabolic profiles [211], the activation of autophagy via the AMPK/SIRT1 pathway [212] and the regulation of macrophage activation and their phenotypic changes [213]. TSF treatment has been found to decrease lipid accumulation, lessen inflammation, and enhance insulin resistance and the integrity of the intestinal barrier [211,212]. Collectively, these findings suggest that TSF is a promising therapeutic option for NAFLD, functioning as a modulator of gut microbiota and metabolic profiles while also affecting hepatic cellular processes to reduce steatosis and related metabolic issues.

Curcumin

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Curcumin, a natural polyphenol, appears to be a promising candidate for the treatment of NAFLD. Research indicates that curcumin supplementation can lower liver fat levels, enhance lipid profiles, and reduce insulin resistance in patients with NAFLD[214]. The beneficial effects of curcumin are linked to its properties as an antioxidant, anti-inflammatory agent, and its ability to prevent fat accumulation [215]. From a mechanistic standpoint, curcumin inhibits the O-GlcNAcylation pathway, promoting antioxidant responses in NASH mice [216]. Furthermore, curcumin improves mitochondrial function via the SIRT3 pathway, reducing liver fat accumulation in postnatal overfed rats and fatty L02 cells[217]. These results imply that curcumin may represent an effective therapeutic option for NAFLD, targeting various components of the disease's underlying mechanisms. Nevertheless, despite substantial experimental support, clinical evidence is still scarce, highlighting the necessity for more human studies to comprehensively determine curcumin's effectiveness in treating NAFLD.

Dihydromyricetin

Dihydromyricetin (DHM) has demonstrated encouraging effects in the treatment of NAFLD. Research suggests that DHM improves NAFLD by managing lipid and glucose metabolism, diminishing inflammation, and restoring the balance of gut microbiota [218,219]. DHM inhibits inflammatory signaling pathways, specifically TLR4/NF-κB, while promoting the growth of beneficial gut bacteria[219]. Additionally, it boosts mitochondrial function and redox equilibrium through SIRT3-dependent pathways, enhancing both mitochondrial respiratory capacity and antioxidant functions [219,220]. Laboratory studies indicate that DHM shields hepatocytes from lipid buildup and oxidative stress induced by oleic acid by inhibiting lipogenesis and modulating the PPARγ, AMPK, and AKT signaling pathways [221].These results imply that DHM has the potential to serve as a therapeutic option for NAFLD, targeting various factors involved in the disease's development, such as lipid metabolism, inflammation, oxidative stress, and gut microbiota imbalance.

b. Sirtuin Inhibitors

AK-7

In the realm of hepatocellular carcinoma, the pharmaceutical sector has explored the potential of sirtuin-targeting compounds, such as the SIRT2 inhibitor AK-7, which has shown anti-tumor effects in preclinical models of HCC [222]. However, the therapeutic potential of SIRT2 inhibition remains contentious, with some studies suggesting both tumor-promoting and tumor-suppressing effects [223,224].

8. Gut Microbiota-Based Interventions: Probiotics, Prebiotics, and Synbiotics

Alongside sirtuin-targeted therapies, the pharmaceutical field is exploring gut microbiota-based interventions for disease management. Strategies addressing dysbiosis encompass FMT, probiotics, prebiotics, and dietary modifications. [225]. Probiotics are beneficial live microorganisms, whereas prebiotics are selective substrates for host microorganisms [226]. These components can influence gut microbiota, improve immune response, and alleviate various health conditions, including gastrointestinal disorders, allergies, and infections [227]. The combined application of probiotics and prebiotics, referred to as synbiotics, demonstrates positive effects on the maintenance of a healthy gut microbiome [228]. Probiotics, prebiotics, and synbiotics have exhibited effectiveness in modulating immune responses, treating infections, managing inflammatory bowel diseases, and augmenting cancer treatment modalities [229].

In NAFLD, FMT is a novel strategy to modify gut microbiome and achieve metabolic balance [77]. FMT entails transferring a healthy microbiome to individuals with dysbiosis. The main aim is to replenish the recipient's gut with beneficial microbes and restore a balanced microbial population [230]. FMT has shown promise in improving intestinal structure and function, enhancing lipid

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metabolism, reducing insulin resistance, suppressing inflammation, and alleviating NAFLD symptoms [231,232]. Figure 6.

By diversifying sirtuin-targeting and gut microbiome-modulating interventions, the pharmaceutical industry seeks to offer enhanced and individualized treatment modalities for various diseases, capitalizing on the intricate interactions between these biological pathways and their health ramifications.

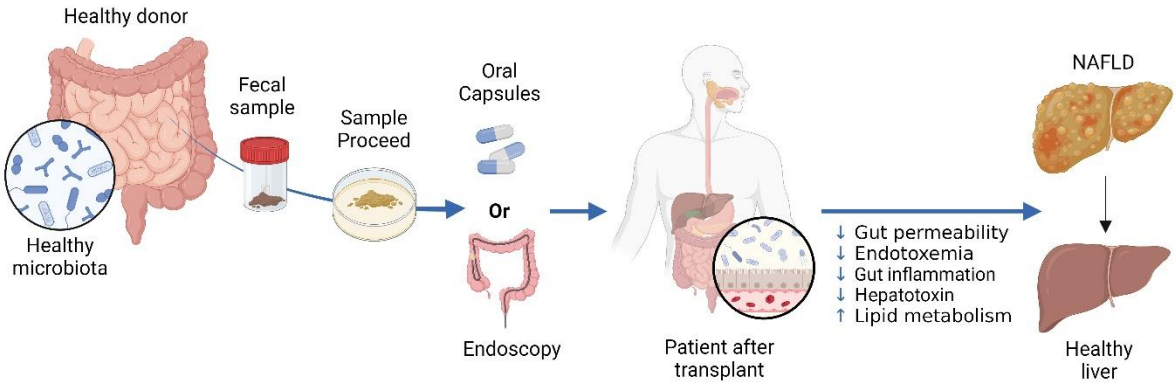

Figure 6. The Use of Fecal Microbiota Transplantation (FMT) in Treating NAFLD.

In FMT, a healthy donor's stool is processed and given to a NAFLD patient. Delivery can be via oral or endoscopic methods. NAFLD is linked to gut dysbiosis and heightened intestinal permeability, facilitating the transfer of gut-derived factors to the liver, exacerbating the condition. FMT seeks to rectify dysbiosis and enhance the gut barrier, aiming to improve liver health in NAFLD individuals.

Conclusions

The intricate interplay between sirtuins and gut microbiota represents a critical nexus in the regulation of metabolic health and disease. As pivotal regulators of cellular mechanisms, sirtuins significantly affect the composition and functionality of gut microbiota, while concurrently serving an essential role in preserving the integrity of the gut barrier and modulating immune responses. Conversely, metabolites derived from gut microbiota can impact sirtuin activity, establishing a dynamic feedback loop that influences overall health outcomes. Given the rising prevalence of NAFLD and its progression to HCC, understanding the molecular mechanisms underlying these interactions plays a key role in creating targeted therapeutic interventions. This review underscores the potential for novel interventions that modulate sirtuin and microbiota pathways to improve health outcomes. Future research should focus on elucidating the detailed mechanisms of sirtuin-microbiota interactions and exploring their implications for innovative approaches to preventing and treating metabolic disorders and liver cancer.

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