Heliyon 10 (2024) e26991

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Short-chain fatty acids in nonalcoholic fatty liver disease: New prospects for short-chain fatty acids as therapeutic targets

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ARTICLE INFO

Keywords:
Nonalcoholic fatty liver disease
Gut microbiota
Short-chain fatty acids
Genetic mechanisms
Epigenetic mechanisms

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is a stress-induced liver injury related to heredity, environmental exposure and the gut microbiome metabolism. Short-chain fatty acids (SCFAs), the metabolites of gut microbiota (GM), participate in the regulation of hepatic steatosis and inflammation through the gut-liver axis, which play an important role in the alleviation of NAFLD. However, little progress has been made in systematically elucidating the mechanism of how SCFAs improve NAFLD, especially the epigenetic mechanisms and the potential therapeutic application as clinical treatment for NAFLD. Herein, we adopted PubMed and Medline to search relevant keywords such as 'SCFAs', 'NAFLD', 'gut microbiota', 'Epigenetic', 'diet', and 'prebiotic effect' to review the latest research on SCFAs in NAFLD up to November 2023. In this review, firstly, we specifically discussed the production and function of SCFAs, as well as their crosstalk coordination in the gut liver axis. Secondly, we provided an updated summary and intensive discussion of how SCFAs affect hepatic steatosis to alleviate NAFLD from the perspective of genetic and epigenetic. Thirdly, we paid attention to the pharmacological and physiological characteristics of SCFAs, and proposed a promising future direction to adopt SCFAs alone or in combination with prebiotics and related clinical drugs to prevent and treat NAFLD. Together, this review aimed to elucidate the function of SCFAs and provide new insights to the prospects of SCFAs as a therapeutic target for NAFLD.

1. Introduction

The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing worldwide and becoming the leading cause of chronic liver disease in developed countries. However, to date, the specific mechanisms leading to NAFLD remain elusive. With the deepening of NAFLD research, it became clear that the two-strike theory could not effectively explain the interactions between genetics and the environment, the effects of microorganisms in the body, and the interactions between different organ systems. Therefore, the multiple-strike theory gradually became widely accepted [1]. In the multiple hits theory, dysbiosis of the gut microbiota (GM) has been identified as one of the factors necessary to influence the development of NAFLD [2]. The liver and intestines are closely related

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https://doi.org/10.1016/j.heliyon.2024.e26991
Received 14 November 2023; Received in revised form 28 December 2023; Accepted 22 February 2024
Available online 27 February 2024

anatomically and functionally, and both develop from the same germ layer in the embryo. The enterohepatic axis subtly links the liver to the intestines, and it is precisely the existence of this enterohepatic axis that allows, under certain pathological conditions, the migration of intestinal bacteria to the liver through the portal vein, leading to an abnormal activation of the immune system, resulting in an inflammatory response and injury [3,4].

Intriguingly, short-chain fatty acids (SCFAs) as the metabolites of bacterial fermentation of intestinal dietary fiber, are the key factors in inhibiting NAFLD progression through portal vein branches [5]. Numerous studies have shown that SCFAs exerted a wide spectrum of positive effects. Shimizu et al. revealed that SCFAs acted as signalling molecules that link gut conditions to physiological metabolism [6]. Leung et al. found that SCFAs maintained the homeostasis of gut barrier and the integrity of gut mucosa, preventing some toxic substances and inflammatory mediators from entering the liver [7]. Thus, SCFAs play a vital role in alleviating of NAFLD.

A growing number of reviews began to report the function about SCFAs in NAFLD. Zhang et al. mainly emphasized the crosstalk between SCFAs and host metabolism in relation to NAFLD pathophysiology [8]. Forlano et al. preferred to focus on SCFAs produced by GM as a potential direction for liver disease [9]. Amiri et al. specialized in potential effects of butyrate on NAFLD [3]. Park et al. tended to identify the dietary fiber and GM as essential carbon sources for hepatic fat synthesis during the development of NAFLD [10]. However, rare reviews systematically summarized the complex mechanisms of SCFAs in mitigation of NAFLD and their detail therapeutic application.

Herein, we perform this review to concluding the complex mechanism of SCFAs in hepatic metabolism at the genetic and epigenetic levels, and propose a promising future direction to adopt SCFAs alone or in combination with prebiotics and related clinical drugs to alleviate NAFLD, which provides a theoretical basis for the clinical intervention and treatment of NAFLD.

2. SCFAs-generation and function

SCFAs are produced in the colon, mainly including acetate, propionate, butyrate, and valerate. The proportions of acetate, propionate and butyrate are highest, with a ratio of 3:1:1, respectively (Table 1). SCFAs are derived from the conversion of pyruvate produced by the GM through glycolytic, acetyl-CoA, lactic acid or succinic acid pathways under the action of intestine [8]. SCFAs are rare in our daily diet, mainly derived from GM fermentation of dietary fibre. Different GM can produce different SCFAs [11,12]. For instance, Bifidobacterium and Streptococcus produce acetate, while Dalister succinatiphilus and Enteric bacteria generate propionate and butyrate [13–15]. Specifically, researchers have observed GM that produce SCFAs in different models of NAFLD (Table 2). In the mice model, Hong et al. found that Astragalus polysaccharides (APS) enriched *D. vulgaris* is effective on attenuating hepatic steatosis possibly through producing acetic acid, and modulation in hepatic lipids metabolism [16]. For rats model, Zhao et al. showed that rats treated with sodium alginate (SA) had significantly increased levels of fecal SCFAs, decreased serum lipopolysaccharide (LPS) levels, attenuated hepatic steatosis and the abundance of Colidextribacter and Oscillibacter was higher in rats of high fatty diet with 150 mg/kg/d sodium alginate group (HAS) compared to rats of high-fat diet group (HFD) [17]. In addition, in a randomized controlled trial, a total of 96 patients with NAFLD were selected as research subjects. And Clostridium butyricum capsules combined with rosuvastatin can effectively improve liver function damage in NAFLD patient [18]. This accumulating evidence further suggests that SCFAs show good therapeutic efficacy in NAFLD in both animal and clinical trials.

SCFAs are incredibly critical for regulating NAFLD progression, mainly through five pathways (Fig. 1). First of all, SCFAs are natural inhibitors of histone deacetylases (HDACs) in T cells, modulating inflammation by suppressing the immune response of T cells [22]. Moreover, SCFAs interact with G protein-coupled receptors (GPCRs, GPR41, GPR43, GPR109A), which are expressed in gut epithelium and immune cells [23]. For example, SCFAs activate GPR41 and GPR43 to act on the surface of intestinal endocrine L cells to promote glucagon-like peptide-1 (GLP-1) secretion, inhibit gastrointestinal peristalsis and gastric juice secretion, thereby controlling appetite and intake to affect lipid oxidation in the liver [24–26]. Meanwhile, SCFAs activate brown adipose tissue, affect energy expenditure and anti-obesity [27]. SCFAs also regulate liver mitochondrial function, inhibit fat accumulation and reverse

Table 1
Classification, source, component content, main signal receptors, and signalling modes of SCFAs.

Classification of SCFAs	The content of the individual parts in SCFAs	Related microbes	SCFAs receptors	Signalling mechanisms
Acetate	60%	Enteric bacteria, Lactis GCL 2505, Human-derived *Bifidobacterium breve* UCC2003, *Bifidobacterium longum* NCIMB 8809 [12,19,20]	FFAR2 (GPR43) FFAR3 (GPR41)	Histone Deacetylases (HDACS)
Propionate	20%	Firmicutes and Bacteroidetes [12]	FFAR2 (GPR43) FFAR3 (GPR41)	
Butyrate	20%	Enteric bacteria, *Eubacterium hallii*, *Ruminococus bromii* [15,21]	FFAR2 (GPR43) FFAR3 (GPR41) GPR109A	G Protein-Coupled Receptors (GPCRS)

Abbreviations: SCFAs, short-chain fatty acids; GPR41, G protein-coupled receptor 41; GPR43, G protein-coupled receptor 43; GPR109A, G protein-coupled receptor 109A; HDACs, histone deacetylases; GPCRs, G protein-coupled receptors.

Table 2
Beneficial SCFAs produced by bacteria in different NAFLD model.
Abbreviations: FASN, fatty acid synthase; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HFD, high-fat diet; ALT, alternative lengthening of telomeres; TNF-α, tumor necrosis factor alpha.

Model	Probiotics	Types of SCFAs	Treatment effect	Study
Male C57BL/6J mice	*D. vulgaris*	Acetic acid	suppressed hepatic FASN and CD36 protein expression, attenuating hepatic steatosis	Hong et al. [16]
	F. prausnitzii	Butyric Acid	upregulated tryptophan metabolism, glutathione metabolism, and valine, leucine, and isoleucine degradation	Hu et al.[103]
	Akkermansia muciniphila	Butyric Acid /Acetic acid/Propionic acid	improved lipid metabolism, such as reducing levels of TG and LDL-C and inhibiting expression of lipogenesis genes	Wang et.al [104]
	Allobaculum/ Bacteroides /Dubosiella	Butyric Acid /Acetic acid/Propionic acid	alleviated liver pathological changes, reduced fat accumulation, and improved oxidative stress in HFD mice	Peng et.al [105]
Male Sprague–Dawley rats	*Butyricicoccaceae_UCG_009, Colidextribacter*	Butyric Acid /Acetic acid/Propionic acid	reduced their body weight, hepatic steatosis, TG, ALT and TNF-α levels	Zhao et.al [17]
NAFLD patients	*Clostridium butyricum*	Butyric Acid	improved intestinal flora balance, reduced blood lipid levels and alleviated liver fibrosis and liver function damage	Zhu et.al [18]

insulin resistance [28]. It is also essential for SCFAs to maintain homeostasis of energy cycle in the body and promote metabolic homeostasis of the liver [29].

Together, SCFAs play inimitable roles in preventing the development of NAFLD through various pathways, which is of significance for providing new strategies for early diagnosis and target treatment of NAFLD.

3. SCFAs coordinate crosstalk in the gut and liver

As a “new virtual metabolic organ”, the gut-liver axis, has received increasing attention in recent years [4,30]. The gut-liver axis refers to a bidirectional relationship established between the gut and the liver through the portal circulation [31]. Although GM mainly exist in the intestine, they also regulate liver function via microbial components and metabolites, acting on the liver through the gut-liver axis [32]. Due to the bidirectional communication of the gut-liver axis, the liver may continue to be influenced by gut derived metabolites and components. Research has revealed that distruption of the gut barrier allowed harmful substances such as LPS, ethanol and other toxic media to enter the liver, which damage liver function. Accumulating evidence shown that SCFAs maintained the integrity of gut barrier by regulating hypoxia-inducible factor (HIF), enhancing intestinal tight junctions, and immune cell activity. The detailed protection mechanisms of SCFAs are shown in Fig. 2.

First, butyrate increases the level of HIF in epithelial cell lines, and the stability of different levels of HIF is crucial for enhancing the epithelial barrier [33]. Kelly et al. reported that butyrate treated can enhance the barrier function of HIF-1β knockdown cells, demonstrating the compensatory function of SCFAs on HIF [34]. Regrettably, the specific mechanisms of SCFAs and HIF are still unclear. Moreover, butyrate also can selectively upregulate tight junction protein claudin-1 and zonula occludens-1, activating the Akt signalling pathway to promote epithelial barrier [35]. Finally, the acetate/GPR43 pathway stimulates potassium efflux and hyper-polarization in HT-29 colon cells, thereby activating inflammatory NOD-like receptor thermal protein domain associated protein 3 (NLRP3) to protect the gut barrier [36]. It is well known that the barrier function of epithelial cells is the first line of defence of the intestine. Therefore, SCFAs can serve as protective messengers for the “first line of defence”, inhibiting the inflammatory response of the liver, and alleviating the occurrence and development of NAFLD.

4. Molecular mechanisms of SCFAs in the protection against hepatic steatosis in NAFLD

Hepatic steatosis is a disease characterized by excessive accumulation of lipids in the liver, mainly in the form of triglycerides (TGs),

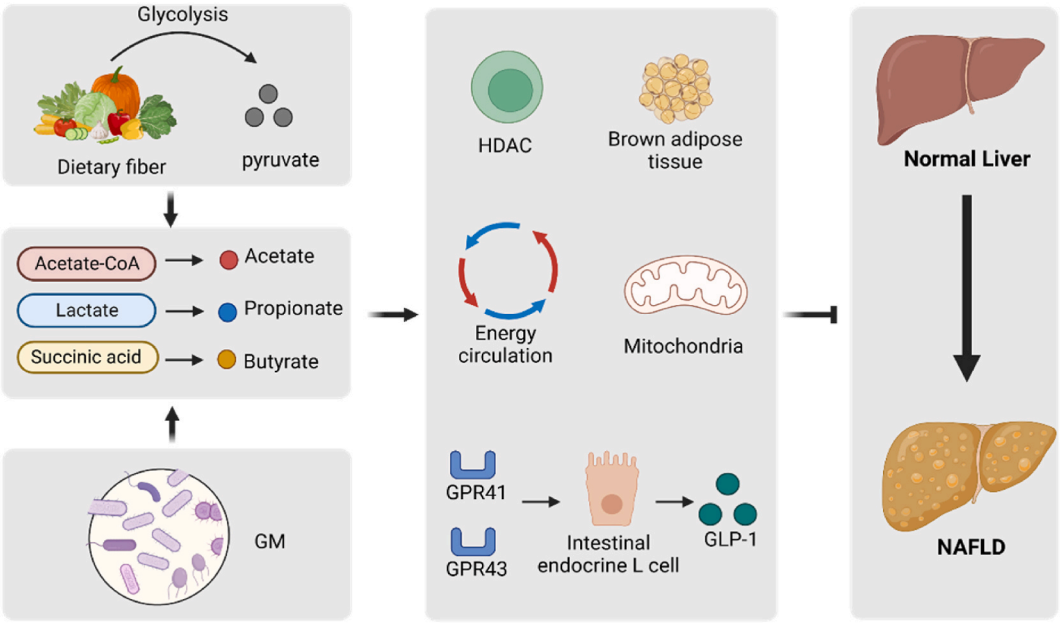

Fig. 1. Generation and function of SCFAs.
GM converts dietary fibre into pyruvate by glycolysis, then converts pyruvate into acetate, propionate, and butyrate through acetyl CoA, lactic acid and succinate pathways, respectively. Firstly, SCFAs as inhibitors of HDACs regulate inflammatory response of NAFLD. Secondly, SCFAs bind to GPR41 and GPR43 to promote intestinal endocrine L cells secretion of GLP-1 to restrain hepatic steatosis. Thirdly, SCFAs stimulate brown adipose tissue to improve NAFLD. Fourthly, SCFAs regulate liver mitochondrial function to improve NAFLD. Fifthly, SCFAs maintain energy circulation of body and promote hepatic metabolic balance. GM, gut microbiota; SCFAs, short-chain fatty acids; NAFLD, Nonalcoholic fatty liver disease; HDAC, histone deacetylase; GPR41, G protein-coupled receptor 41; GPR43, G protein-coupled receptor 43; GLP-1, glucagon-like peptide-1.

which is an important hallmark of NAFLD [37,38]. Here, we summarize various functions of SCFAs during hepatic steatosis progression, which contribute to understand the potential role of SCFAs in the progression of NAFLD and provides potential targets for the treatment of NAFLD (Table 3).

4.1. SCFAs reduce cholesterol to modulate hepatic steatosis

The liver is the central organ that regulates systemic cholesterol homeostasis, and abnormal cholesterol metabolism in hepatic not only lead to NAFLD progression, but also drive the development of atherosclerotic dyslipidemia [52]. Recent studies have revealed that in the high-cholesterol diet (HCD) induced NAFLD hamster model, acetate, propionate and butyrate significantly reduced total cholesterol (TC) by 24%, 18% and 17%, respectively, further demonstrating the central role of SCFAs in cholesterol reduction [40]. However, it remains unclear how SCFAs regulate cholesterol synthesis and secretion, and little is known about the mechanisms.

Here, we summarized five potential pathways for SCFAs to reduce cholesterol. First, SCFAs inhibit gene expression in the cholesterol synthesis pathway through sterol regulatory element binding protein-1 (SREBP-1) (Fig. 3a), of which *SREBP-1* plays a key role in regulating fatty acid synthesis in the liver [53,54]. Fushimi et al. reported that acetic acid reduced the supply of acetyl-CoA (a substrate of cholesterol) by reducing mRNA level and activity of ATP citrate lyase (ATP-CL) caused by the suppression of *SREBP-1* gene expression [39]. Second, SCFAs promote the conversion of cholesterol into bile acids (BAs) to reduce cholesterol levels by upregulating cholesterol 7α-hydroxylase (CYP7A1) expression (Fig. 3b). CYP7a1 is the key rate-limiting enzyme that converts cholesterol to BAs. Zhao et al. further confirmed that adding Ac, Pr or Bu to diet can significantly increase the expression of *CYP7A1* and promote fecal excretion of BAs to reduce cholesterol levels [40]. Third, SCFAs play a vital role in accelerating cholesterol transport from the liver by regulating ATP binding cassette transporter protein A1 (ABCA1) (Fig. 3c). Based on animal studies, Du et al. found that butyrate treatment significantly inhibited HFD-induced atherosclerosis and hepatic steatosis by promoting ABCA1-mediated cholesterol efflux from macrophages [42]. In addition, SCFAs enhance the effectiveness of apolipoprotein A1 (ApoA-1) modification to promote cellular cholesterol efflux through the ABCA1 pathway [43,55]. Fourth, SCFAs reduce cholesterol levels by regulating the expression of cholesterol transport proteins such as Niemann-Pick C1-like 1 (NPC1L1) and ATP-binding cassette transport proteins G5 and G8 (ABCG5/8) (Fig. 3d). The NPC1L1 plays a vital role in intestinal cholesterol absorption, while ABCG5/8 mainly responds to cholesterol efflux in the duodenum [44]. Yamanashi et al. reported that coincubation of Caco-2 cells (a human intestinal cell line) with butyrate downregulated the expression of *NPC1L1* but increased the mRNA level of *ABCG5/8* [45]. Fifth, SCFAs act on GPR43 to mediate the leptin response in controlling cholesterol levels (Fig. 3e). Leptin is a signalling molecule that reduces hepatic lipogenesis and cholesterol synthesis by inhibiting the expression of *SREBP-1* and cholesterol-related genes, thereby reducing cholesterol levels and alleviating hepatic steatosis [56,57].

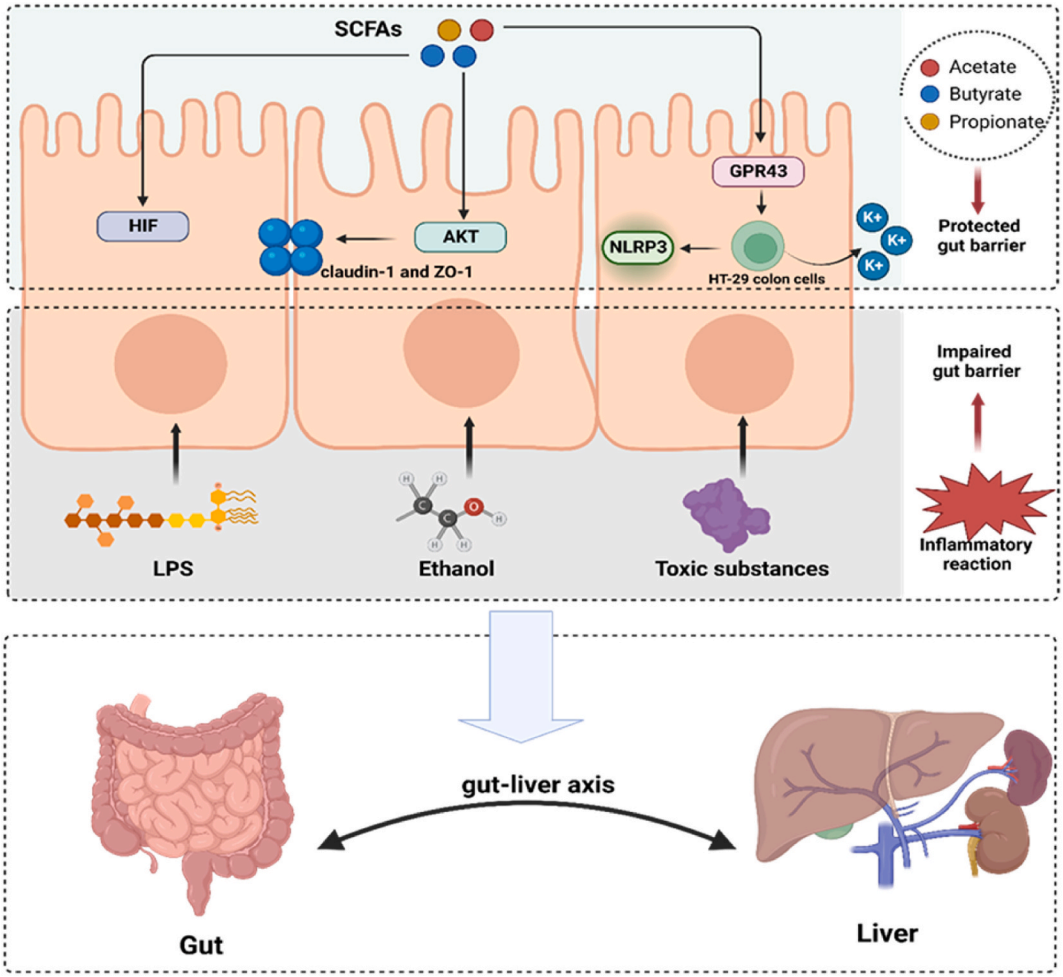

Fig. 2. SCFAs play a protective role as an intestinal barrier. Ethanol, LPS and toxic substances act on the intestinal epithelial barrier which could trigger an inflammatory response and cause damage to the intestinal barrier. Butyrate upregulates HIF target gene expression to enhance the epithelial barrier. Butyrate might enhance the abundance of tight junction proteins claudin-1 and ZO-1 through activation of Akt/mTOR mediated protein synthesis, which enhance the epithelial barrier. SCFAs bind GPR43 on colonic epithelial cells to stimulates K (+) efflux and hyperpolarization, which lead to NLRP3 inflammasome activation. The inflammasome pathway maintain the integrity of the intestinal barrier by ensuring the repair and cell survival under stress conditions. LPS, lipopolysaccharide; HIF, hypoxia-inducible factor; ZO-1, zonula occludens-1; GPR43, G protein-coupled receptor 43; NLRP3, NOD-like receptor thermal protein domain associated protein 3.

In conclusion, SCFAs reduce cholesterol levels to alleviate hepatic steatosis through genes such as *SREBP-1*, *ATP-CL*, *CYP7A1*, *ABCA1*, *NPC1L1* and *ABCG5/8* to improve NAFLD.

4.2. SCFAs induce autophagy to regulate hepatic steatosis

Research has implied that SCFAs alleviate NAFLD progression by activating the autophagy pathway. Autophagy is imperative for intracellular homeostasis and plays an instrumental role in the progression of NAFLD via mediating metabolic regulation, maintaining lipid homeostasis, and suppressing hepatic inflammation [58,59]. SCFAs induce uncoupling protein 2 (UCP2)-mediate autophagy of hepatocytes to improve hepatic steatosis [60]. Propionate and butyrate in SCFAs could directly induce hepatic autophagy through the activation of peroxisome proliferator-activated receptor γ (PPARγ), leading to the transcription *UCP2*. In addition, the increased activity of *UCP2* result in the uncoupling of the respiratory chain, which in turn reducing hepatic ATP and activating the 5′-adenosine monophosphate-activated protein kinase (AMPK) pathway and autophagy [46]. In brief, SCFAs induce liver autophagyvia the PPARγ-UCP2-AMPK pathway to alleviate the development of NAFLD, which may become a new therapeutic strategy.

4.3. SCFAs regulate hepatic steatosis through GPCRs

GPCRs are the largest receptor family in humans and the most successful drug targets in history, regulating the physiological

Table 3
Target genes and related signalling pathways activated by SCFAs.

Target genes	Complexes/pathway	Function	References
SREBP-1	ATP-CL	Reducing the supply of substrate	[39]
CYP7A1	/	Promoting the conversion of cholesterol into bile acids	[40]
SREBP2	/	Augmenting cholesterol uptake in vascular cells	[40,41]
LDLR	/	Augmenting cholesterol uptake in vascular cells	[40,41]
ABCA1	/	Accelerating cholesterol transport from the liver	[42]
ApoA-1	/	Promoting cellular cholesterol efflux	[43]
NPC1L1	/	Playing a vital role in intestinal cholesterol absorption	[44]
ABCG5/8	/	Promoting cholesterol efflux from the duodenum	[44,45]
UCP2	AMPK	Inducing liver autophagyvia	[46]
PPARγ	UCP2	Inducing liver autophagyvia	[46]
FFAR2	TNF-α, Gi	Reducing the inflammatory response of the liver and inhibiting lipolysis and plasma FFA levels	[47,48]
FFAR3	PPARα	Affecting lipid metabolism	[49]
GPR109A	/	Improving the hepatic inflammatory response	[50,51]

Abbreviations: SREBP-1, sterol regulatory element binding protein-1; CYP7A1, cholesterol 7α-hydroxylase; SREBP2, sterol regulatory element-binding protein 2; LDLR, LDL receptor; ABCA1, ATP binding cassette transporter protein A1; ApoA-1, apolipoprotein A1; NPC1L1, Niemann-Pick C1-like 1; ABCG5/8, ATP-binding cassette transport proteins G5 and G8, GPR43, G protein-coupled receptor 43; UCP2, uncoupling protein 2; AMPK, activating the 5′-adenosine monophosphate-activated protein ktinase; PPARγ, peroshorthorxisome proliferator-activated; receptor γ, FFAR2, free fatty acid receptor 2; TNF-α, tumor necrosis factor alpha; FFAR3, free fatty acid receptor 3; PPARα, pshort-chaineroxisome proliferator-activated receptor α; GPR109A, G protein-coupled receptor 109A

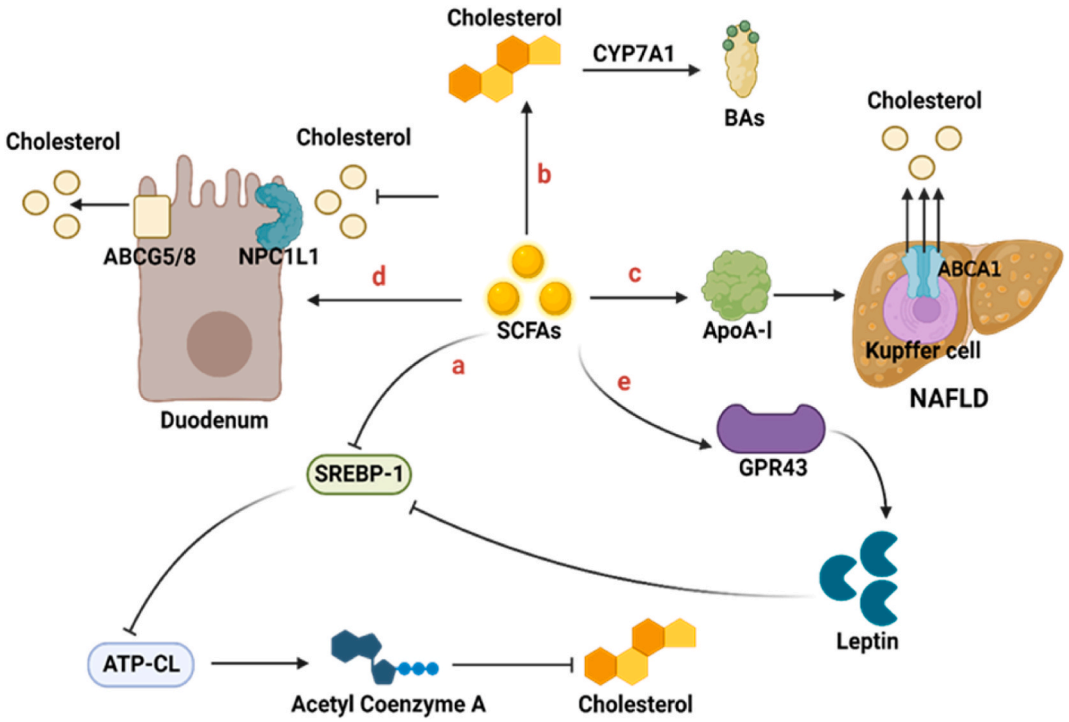

Fig. 3. The mechanism of SCFAs madiate a decrease in cholesterol levels. (a) SCFAs down-regulate gene expression in the cholesterol synthesis pathway through *SREBP-1*. (b) SCFAs promote the conversion of cholesterol into BAs by upregulating the expression of *CYP7A1*, thereby reducing cholesterol levels. (c) SCFAs accelerate cholesterol export and transport cholesterol out of the Kupffer cell in the NAFLD by regulating ApoA-I to affect *ABCA1*. (d) *NPC1L1* abundantly expresses in the duodenum and mediates cholesterol absorption, while *ABCG5/8* forms heterodimers, leading to cholesterol efflux. SCFAs downregulate *NPC1L1* expression and upregulate *ABCG5/8* expression, thereby reducing cholesterol levels. (e) SCFAs act on GPR43 to stimulate leptin production and inhibit *SREBP-1* expression, thereby down-regulating cholesterol levels. SCFAs, short-chain fatty acids; SREBP-1, sterol regulatory element binding protein-1; Bas, bile acids; CYP7A1, cholesterol 7α-hydroxylase; NAFLD, Nonalcoholic fatty liver disease; ABCA1, ATP-binding cassette transporter protein A1; NPC1L1, Niemann-Pick C1-like 1; ABCG5/8, ATP-binding cassette transport proteins G5 and G8; GPR43; G protein-coupled receptor 43.

functions of almost all tissues and cells throughout the body [61,62]. GPCRs specifically bind substances in the extracellular environment, including hormones, chemokines, lipids, and proteins. Presently, the main receptors for SCFAs in the GPCRs family are GPR41, GPR43, and GPR109A. Among them, GPR41 and GPR43 are the most important receptors for SCFAs that also named free fatty

acid receptor 3 (FFAR3) and free fatty acid receptor 2 (FFAR2), respectively. The schematic diagram of the interaction between SCFAs and their GPCRs in the gut and liver are shown in Fig. 4. FFAR2 can be activated by stimulating SCFAs in anti-inflammatory M2 macrophages, the expression of which contributes to upregulate tumor necrosis factor-α (TNF-α) expression to reduce the inflammatory response of the liver [47] (Fig. 4a). Besides, acetate and propionate act as external signalling molecules specifically binding to the FFAR2 receptor, coupling it to the Gi pathway in adipocytes and inhibiting lipolysis and plasma FFA levels [48]. Moreover, plasma SCFAs may indirectly affect lipid metabolism related genes in the liver through the expression FFAR3 in other tissues, such as fatty acid synthase (Fas) and peroxisome proliferator-activated receptor α (PPARα) in the liver (Fig. 4b). Additionally, in the research of Samuel et al., FFAR3 knockout mice gained less weight than wild-type mice, but this difference disappeared under germ-free conditions [63]. Therefore, SCFAs are likely to mediate this differential change through the change of FFAR3. With a deeper understanding of SCFAs, it became known that SCFAs activate GPR109A to induce differentiation of Treg cells and T cells that produce interleukin 10 (IL-10), thereby improving hepatic lipid degeneration [50] (Fig. 4c). It has been reported that butyrate increased the Regulatory cell (Treg) population of adipose tissue in obese mice via GPR109A signalling, which contributed to improving the hepatic inflammatory response [51]. Altogether, leveraging GPR signals in the treatment of liver metabolic diseases is a potential research field that deserves further investigation.

5. Epigenetic mechanisms of SCFAs in improving NAFLD

Epigenetic includes DNA methylation, histone modification, microRNA (miRNA) regulation, and chromosome remodeling [64]. NAFLD is a representative metabolic disease that is susceptible to environmental factors and epigenetic modifications. Epigenetic modifications integrate microbial signals to calibrate host cell transcriptional programs without altering the underlying genetic code [65]. In particular, microbial metabolites derived from the diet (e.g., SCFAs) can produce epigenetically modified substrates and enzyme regulators [66]. The specific mechanisms of SCFAs inducing epigenetic modifications are depicted in Fig. 5.

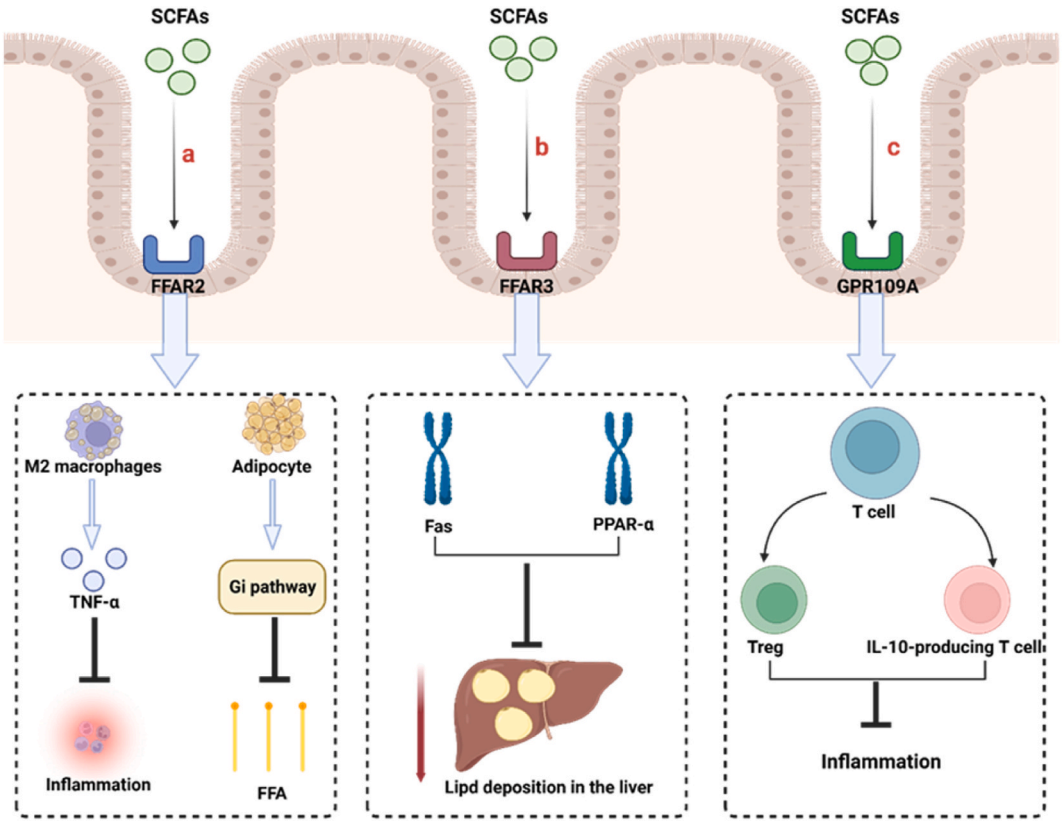

Fig. 4. SCFAs bind with FFAR2, FFAR3 and GPR109A to improve hepatic steatosis, respectively. (a) SCFAs stimulate FFAR2 to activate M2 macrophages, which upregulate TNF-α expression and inhibit liver inflammation. Meanwhile, under the action of SCFAs, FFAR2 can decrease FFA content to improve hepatic steatosis by Gi pathway. (b) SCFAs activate FFAR3 to down-regulate lipid synthesis genes (*Fas* and *PPARα*). (c) SCFAs induce T cell differentiation into Treg cells and IL-10-producing T cells via GPR109A signalling, which alleviate liver inflammation. SCFAs, short-chain fatty acids; FFAR2, free fatty acid receptor 2; TNF-α, tumor necrosis factor-α; FFA, Free fat acid; FFAR3, free fatty acid receptor 3; GPR109A, G protein-coupled receptor 109A.

5.1. DNA methylation

The change in DNA methylation induced by SCFAs is an important epigenetic modification [67]. During the occurrence and development of NAFLD, the hypo-and hypermethylation genes such as growth factor-α (*PDGFα*), phospholipase C gamma 1 (*PLCG1*), caspase 1 (*CASP1*) are epigenetic regulated and exacerbate the progression of NAFLD by participating in immune response, oxidative stress, and liver lipid degeneration [68]. It is notably that SCFAs reduce the expression of DNA methyltransferases 1 (*DNMT1*) and methyl CpG binding structural domain protein 2 (*MBD2*), inhibiting the binding of these enzymes toadiponectin and resistin promoters. Among them, adiponectin and resistin are the main adipokines secreted by white adipose tissue, and their abnormal expression promotes the progression of NAFLD [69,70] (Fig. 5a). The expression of adiponectin and resistin are upregulated in the liver of mice fed with high-fat diet and treated with antibiotics, as well as genes related to fat oxidation and heat production, such as *PPARα,* peroxisome proliferator-activated receptor-γ coactivator-1α (Pgc-1α), and increased adipose triglyceride lipase (Atgl) in the liver [71–73]. The potential mechanism is that antibiotics reduce the number of GM producing SCFAs. In addition, SCFAs upregulate the expression of adiponectin and resistin mRNA and restored it due to the reduced in DNA methylation at the gene promoter.

5.2. Histone modification

Histone modifications play a key role in the epigenetic regulation of gene expression [74]. Among that, the epigenetic role of SCFAs is mainly to activating acetylation, which acted as HDACs inhibitors has been widely demonstrated [75–77]. SCFAs promote T-cell differentiation by inhibiting the acetylation of p70 S6 kinase promoted by HDAC in T cells, thereby acting as a mechanism target of the rapamycin (mTOR) pathway to regulate inflammatory response in the liver [22] (Fig. 5b). Furthermore, butyrate induces Treg differentiation *in vitro* and *in vivo* by enhancing histone H3 acetylation in the forkhead box p3 (Foxp3) promoter and conserved noncoding

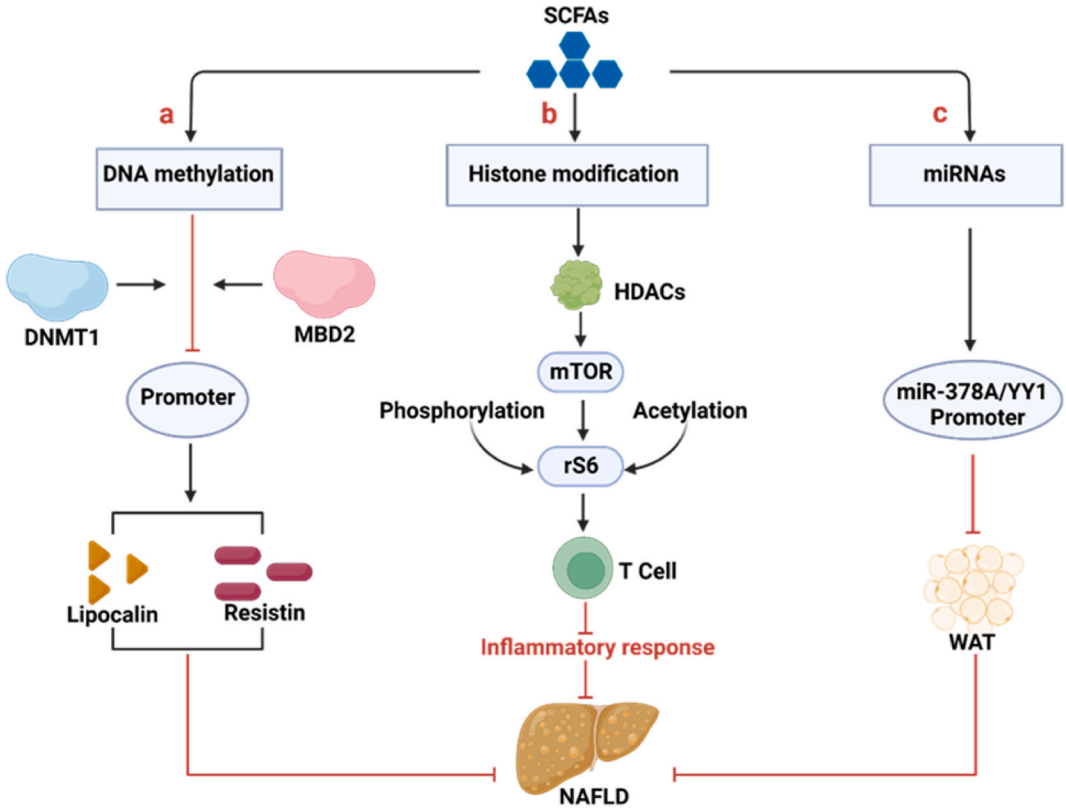

Fig. 5. Possible mechanisms of SCFAs-induced epigenetic modifications to improve NAFLD. (a) SCFAs reduce the DNA methylation portion of the adiponectin and resistin promoters, which was mediated by reducing the expressions of DNMT1 and MBD2, suppressing the binding of these enzymes to the promoters of adiponectin and resistin. The mRNA expression of adiponectin and resistin is upregulated due to demethylation of gene promoter, thus restoring gene transcription. Among them, adiponectin and resistin can effectively improve NAFLD. (b) SCFAs modulate chromatin by inhibiting HDACs to increase acetylation and phosphorylation of the p70 S6 kinase and phosphorylation rS6, while regulating the mTOR pathway required for T-cell production, thereby suppressing the T-cell immune response to regulate metabolic inflammatory responses in the liver. (c) SCFAs inhibit WAT production by regulating the methylation level of the miR-378A/YY1 promoter in the host and the expression of the miR-181. SCFAs, short-chain fatty acids; DNMT1, DNA methyltransferases 1; MBD2, methyl CpG-binding structural domain protein 2; NAFLD, Nonalcoholic fatty liver disease; mTOR, mechanistic target of rapamycin; WAT, white adipose tissue.

sequence region, which may be beneficial for improving liver inflammatory response [78]. Besides, SCFAs effectively can inhibit HDACs, and the higher the concentration, the more significant the effect. Specifically, SCFAs indirectly affect HDACs through the sodium-coupled monocarboxylate transporter-1 (SMCT-1), a transporter that binds to HDACs and FFAR3, thereby inhibiting butyrate-induced histone acetylation [79,80]. Paradoxically, as previously reported, SCFAs regulated chromatin by inhibiting HDACs, but Thomas and Denu demonstrated that SCFAs induced histone acetylation by activating activates histone acetyltransferases (HATs) rather than inhibiting HDACs [81]. Altogether, the evidence for SCFAs in activating acetylation is widely accepted, which may greatly broaden the potential strategies for treating NAFLD.

5.3. MicroRNA

miRNAs are a family of post transcriptional gene inhibitors that do not encode proteins but exert a vital role in regulating gene expression. Studies have revealed that SCFAs influence the development of NAFLD by mediating miRNAs [82] (Fig. 5c). Acetate and butyrate regulate NAFLD progression through the miR-378a-YY1 axis. Overexpression of Yin yang 1 (*YY1*), a direct target gene of miR-378a family, significantly enhances liver lipid metabolism. Meanwhile, acetate and butyrate could affect miR-378a family via regulating the DNA methylation of its promoter [83]. Intriguingly, it is worth noting that Pant et al. provided conclusive evidence that butyrate induces cell apoptosis by regulating miR-22 in hepatic cancer cells [84]. In view of the fact that the advanced stage of NAFLD often progresses to cancer, investigating the role of miR-22 in NAFLD seems provide valuable insights into its mechanism. In summary, SCFAs regulate the metabolic processes of liver by regulating the expression of miRNAs as signalling molecules.

Table 4
Different applications of SCAFs as potential therapy for the treatment of NAFLD.

Categories	Specific measures	Results	References
Individual application	●Administration of sodium butyrate to male C57BL/6J mice at 4–5 weeks of age	●Compared to the control group, TG, IL-6 and TNF-α levels were reduced in the dosing group, as were serum LPS concentrations	[86]
	●Administration of SCFAs to weaned pigs	●LDL-c concentration were significantly reduced and GLP-1, PYY and leptin concentration were increased in dosing group	[87]
	●C57BL/6 mice were administered sodium acetate, sodium propionate or sodium butyrate during 6 weeks feeding period	●The levels of TG, IL-6 and TNF-α decreased in the administered group compared to the control group, as did the serum concentration of LPS	[88]
	●Pigs were treated with 0.1% sodium acetate, 0.1% sodium propionate, 0.1% sodium butyrate, 0.1% mixed SCFAs, respectively	●Compared to the control group, the concentration of TG, TC and LDL-c decreased significantly and the concentration of GLP-1, PYY and leptin increased significantly in the administration group	[89]
Prebiotics application	●In a double-blind, randomized, placebo-controlled crossover design, 14 healthy, overweight obese men were given prebiotic inulin	●Plasma glucose and insulin were lower after inulin ingestion and plasma free fatty acids were higher in the early post-inulin period and lower in the late postprandial period and SCFAs were increased in *vivo*	[90]
	●Male C57BL/6 mice given a high fat/high sugar diet supplemented with 10% FOS for 10 weeks	●Significantly lower TC, TG and LDL levels and increased SCFAs in FOS-supplemented mice	[91]
	●12 weeks SP dietary supplementation for obese mice	●In obese mice, body weight was reduced and serum lipid levels and liver triglyceride levels were also reduced, while SCFAs levels were increased	[92]
Clinical drugs application	●Common carp were exposed to 0, 10, 100, and 250 μM OLA for 60 days	●Decreased TC, LDL, TG, HDL, and increased abundance of SCFA-producing bacteria	[93]
	●Eight-week-old male C57BL/6J mice were randomly divided into five groups, the experimental group was established as a liver fibrosis model and given FTA	●Compared to control group, there was no significant collagen deposition and the GM was altered, with significantly lower levels of LPS, MIP-1α and TNF-α, as well as increased levels of SCFAs in the administered mice	[94]
	●In the NAFLD model group, the Male 4-week-old C57BL/6J mice were divided into three subgroups: NAFLD MG (n = 8, fed by HFD), ECD group (EG, n = 8, fed by HFD and received ECD 5.7 g/kg/d) and SCFAs group	●Both ECD and SCFAs reversed HFD-induced weight gain and serum ALT and AST, which inhibited liver TLR-4, TNF-α, IL-1β and NF-κB levels. ECD inhibited the decrease of IETJ protein induced by HFD and restored HFD-induced impaired SCFAs production	[95]
	●Male C57BL/6 mice were treated with SJP/saline for 6 weeks	● After SJP treatment, TG, TC, ALT, and AST were significantly decreased and the level of PPARγ protein was steadily increased. In addition, SJP treatment regulated the relative abundance of SCFAs - producing bacteria	[96]

Abbreviations: SCFAs, short-chain fatty acid salts; FOS, Fructo-oligosaccharide; SP, seabuckthorn polysaccharide; OLA, Olanzapine; NAFLD, Nonalcoholic fatty liver disease; FTA, Forsythiaside A; ECD, Erchen decoction; SJP, Jiang Powder; TG, triglyceride; TC, total cholesterol; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; LPS, lipopolysaccharide; LDL-c, low-density lipoprotein cholesterol; GLP-1, glucagon-like peptide-1; PYY, Peptide YY; LDL, low-density lipoprotein; HDL, high-density lipoprotein; GM, gut microbiota; MIP-1α, macrophage inflammatory protein-1alpha; TLR-4, toll-like receptor 4; IL-1β, interleukin-1β; NF-κB, nuclear factor-kappaB; IETJ, intestinal epithelial tight junction; HFD, high fatty diet, ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPARγ, peroxisome proliferator-activated receptor γ.

6. Future and outlook: SCFAs as new targets for the treatment of NAFLD

The dysregulation of GM promotes the development of NAFLD, as some bacteria can produce toxic substances, leading to liver inflammation or metabolic disorder [85]. However, as the metabolites of GM, how to link SCFAs with the prevention and treatment of NAFLD remains a crucial issue. Here, we mainly focus on the three potential applications of SCFAs (Table 4), with the aim of providing new targets for the prevention and treatment of NAFLD.

6.1. SCFAs improve NAFLD directly

The use of probiotics to interfere with non-alcoholic steatohepatitis (NASH) may be a novel therapeutic strategy for anti-NAFLD drug discovery. However, due to the susceptibility of probiotics direct administration to environmental and *in vivo* active factors, many studies have adopted SCFAs as supplements, focusing on whether they can improve NAFLD. Currently, butyrate has been widely used in experimental models to improve NAFLD, while clinical research remains scarce due to the difficulty in controlling dosage and duration. In an animal study, Fang et al. showed that sodium butyrate administration altered the composition of HFD-induced intestinal microbiota, improved the gut barrier and lowered serum LPS concentration, further ameliorating lipid accumulation associated with obesity [86]. Nevertheless, it appears that unlike SCFAs administered as a single ingredient, full-ingredient application of SCFAs seems to be more effective in improving liver fat deposition. Jiao *et a*l. reported that oral administration of SCFAs reduced liver fat deposition in weaned pigs by reducing lipogenesis and enhancing lipolysis in different tissues [87]. Deng et al. found that SCFAs treatment significantly reduced alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglyceride and cholesterol levels in mice with methionine and choline deficient (MCD) diet, thereby alleviating hepatic steatosis [88]. Jiao et al. also reported that SCFAs reduced adipogenesis and enhanced lipolysis in different tissues of pigs by regulating hormones and genes [89]. Although SCFAs are rarely used in clinical trials, there has been clear research in recent years indicating a strong correlation between SCFAs and the progression of NAFLD. A clinical trial showed that although the levels of SCFAs in fecal samples of patients with cirrhosis were lower, these functional abnormalities became more pronounced as the severity of liver disease increases [97]. Altogether, the feasibility of SCFAs alone treating NAFLD is of great significance for further investigation.

6.2. Prebiotics as means to increase SCFAs to improve NAFLD

Numerous studies have shown that prebiotics can selectively stimulate the growth and activity of beneficial bacteria in the intestinal tract, thereby alleviate the progression of NAFLD. The potential mechanism of prebiotics for improving NAFLD may attribute to increasing of SCFAs. In 2016, the International Scientific Association of Probiotics and Prebiotics (ISAPP) defined prebiotics as "a beneficial substrate selectively utilized by host microorganisms" [98]. Prebiotics mainly include three types: inulin, fructo-oligosaccharides, seabuckthorn polysaccharide and other polysaccharide. Firstly, inulin is a natural soluble dietary fibre that serves as a reserve biopolysaccharide for plants and is fermented by GM to produce butyrate [99]. Guo et al. reported that inulin-induced GM remodeling led to increased production of SCFA and expression of giopoietin-like protein 4 (ANGPTL4), which improved glucose and lipid metabolism [90]. Similarly, another research revealed that ingesting probiotic inulin improved fat oxidation in obese man while promoting the production of SCFAs in their body [100]. Secondly, Fructo-oligosaccharides (FOSs) are consistence of short fructose chains of various oligosaccharides with different chain lengths. Numerous studies have indicated that FOSs restore normal gastrointestinal microbiota and intestinal epithelial barrier function, and alleviate steatohepatitis [101]. Furthermore, it was found that FOSs intake increased the level of SCFAs in the body and significantly improved hepatic steatosis and inflammatory cell infiltration [102]. FOSs reversed the accumulation of high fat and high sugar (HFS) induced liver lipids *in vivo* by promoting the production of SCFAs by GM, reducing serum lipid levels, and improving HFS induced liver inflammation by promoting the generation of SCFAs by the GM [91]. Thirdly, seabuckthorn polysaccharide (SP) as a typical polysaccharide, which also played a similar role in upregulation of SCFAs to improved liver steatosis. In an experiment based on obese mice, continuous 12 weeks of SP dietary supplements significantly reduced body weight and increased fecal SCFAs, indicating that the regulation of SP on liver lipid metabolism may be induced by changes in GM and increase in SCFAs production [92].

These evidences suggest that prebiotics improve NAFLD by restoring the GM and increasing SCFAs levels, mainly including three types of inulin, fructo-oligosaccharides, seabuckthorn polysaccharide and other polysaccharide. Therefore, compared to administering prebiotics alone, combining prebiotics with SCFAs to improve NAFLD may enhance the therapeutic efficacy to some extent.

6.3. Clinical drugs for upregulating SCFA levels to improve NAFLD

Numerous studies have demonstrated the ability of SCFAs to ameliorate NAFLD, while no definitive medications that can be utilized for the clinical treatment of NAFLD with SCFAs. As a result, researchers have become dedicated to the search for what appears to be the existence of effective drugs for upregulating the expression of SCFAs and thereby ameliorating NAFLD. Now, probiotics have been shown to modulate the gut microbiota and produce SCFAs to inhibit lipid deposition in the liver. Nevertheless, since probiotics are categorized only as nutraceuticals and not as drugs, public acceptance and regulatory rules have also limited their use in the clinical field [103]. Until recently, some researchers have suggested proposing the term "probacine" (PRObiotic BActerial mediCINE) emphasizes the role of probiotics in the prevention, alleviation, and treating diseases, and further promotes the clinical application of probiotics [104]. Therefore, the use of probiotics in clinical medicine to improve NAFLD can be seen as a promising prospect.

In addition to probiotics, a host of approved clinical drugs can also upregulate SCAFs to some extent. Olanzapine (OLA) is a

commonly used drug for the treatment of schizophrenia. OLA exposure altered the composition of carp GM, increased the abundance of SCFAs producing bacteria, and affected lipid metabolism signalling pathways. The potential mechanism can be explained by the regulation of the GM-SCFA-PPAR signalling pathway [93]. Forsythiaside A (FTA) is isolated from the traditional Chinese medicine Forsythiae fructus (Lian Qiao) and is a natural liver protective agent. Studies on mice have shown that FTA can improve liver fibrosis by inhibiting inflammation and oxidative stress, modulating GM and increasing SCFAs levels [94]. Phillygenin (PHI) is also an important fingerprint lignan component of Forsythiae fructus, with has significant liver protection, anti-inflammatory, and antioxidant effects. Wang et al. showed that PHI promoted the production of SCFAs in the intestine of mice and ameliorated carbon tetrachloride induced liver fibrosis [105]. Erchen decoction (ECD) is a classic Chinese herbal formula consisting of citrus reticulate, pine, poria cocos, and ural licorice, which has been widely used to treat NAFLD. Researchers have found that ECD effectively improved NAFLD, leading to a significant increase in SCFAs in faeces. Similar to the former, Sheng-Jiang Powder (SJP) is an empirical traditional Chinese medicine formula for treating NAFLD, commonly used in clinical. Li et al. found that liver lipid deposition in mice was effectively improved after administration of SJP [96]. Next, they further investigated whether there were changes in the gut microbiota of mice. The results were unexpected: the relative abundance of SCFAs producing bacteria was upregulated after SJP treatment.

Therefore, SJP can effectively attenuate HFD-induced NAFLD, which may be due to changes in SCFAs content *in vivo*. Overall, developing clinical drugs to upregulate SCFAs for the treatment of NAFLD seems to be an exciting approach. However, considering the side effects of drugs and patients compliance, it is still necessary to further clarify the safety of drug.

7. Conclusions

SCFAs play an important role in regulating inflammation, glucose and lipid metabolism, which have been revealed as one of the most prevalent therapeutic targets in management of NAFLD. In this review, we specifically discussed the production and function of SCFAs, as well as their crosstalk coordination in the gut liver axis, summarized the potential molecular and epigenetic mechanisms of SCFAs in improving NAFLD, and explained the new prospects of their therapeutic measures. It is worth noting that both direct and indirect use of SCFAs are effective methods for improving NAFLD. And prebiotics and clinical agents that increase the content of SCFAs may be valuable in improving clinical efficacy. However, the following issues still need to be further considered. First, the management of SCFAs as a treatment for NAFLD remains limited due to the lack of clinical data on how SCFAs regulate lipid metabolism. Second, the safety of prebiotics or related clinical drugs remains obscure, and their dosage should be further evaluated based on individual differences to determine potential adverse reactions. Altogether, further consideration of these issues may provide significant progress for the effective application of SCFAs in the prevention and treatment of NAFLD.

Funding

This study was supported by National Natural Science Foundation of China, Grant/Award Number: (82300661); Natural Science Foundation of Anhui province, Grant/Award Number: (2308085QH246); Natural Science Foundation of the Anhui Higher Education Institutions, Grant/Award Number: (KJ2021A0205); Basic and Clinical cooperative research program of Anhui Medical University, Grant/Award Number: (2022xkjT013); Scientific Research Foundation of Anhui Medical University (2023xkj002). Figures created with BioRender.com and published with permission.

Data availability statement

No data was used for the research described in the article.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yaling Zhu reports financial support was provided by National Natural Science Foundation of China. Yaling Zhu reports financial support was provided by National College Students Innovation and Entrepreneurship Training Program. Yaling Zhu reports financial support was provided by Natural Science Foundation of the Anhui Higher Education Institutions. Yaling Zhu reports financial support was provided by Basic and Clinical cooperative research program of Anhui Medical University.

Abbreviations

NAFLD	Nonalcoholic fatty liver disease
GM	Gut microbiota
NASH	Nonalcoholic steatohepatitis
SCFAs	Short-chain fatty acids
APS	Astragalus polysaccharides
SA	Sodium alginate
HFD	High-fat diet group
HAS	HFD with 150 mg/kg/d sodium alginate group
HDAC	Histone deacetylase
GPCRs	G protein-coupled receptors
GPR41	G protein-coupled receptor 41
GPR43	G protein-coupled receptor 43
GPR109A	G protein-coupled receptor 109A
GLP-1	Glucagon-like peptide-1
LPS	Lipopolysaccharide
HIF	Hypoxia-inducible factor
ZO-1	Zonula occludens-1
TGs	Triglycerides
TC	Total plasma cholesterol
HCD	High-cholesterol diet
SREBP-1	Sterol regulatory element binding protein-1
SREBP-2	Sterol regulatory element binding protein-2
ATP-CL	ATP citrate lyase
BAs	Bile acids
ABCA1	ATP-binding cassette transporter protein A1
ApoA-I	Apolipoprotein A1
NPC1L1	Niemann-Pick C1-like 1
ABCG5	ATP-binding cassette transport proteins G5
ABCG8	ATP-binding cassette transport proteins G8
UCP2	Uncoupling protein 2
PPARγ	Peroxisome proliferator-activated receptor γ
AMPK	Adenosine 5‘-monophosphate-activated protein kinase
FFAR3	Free fatty acid receptor 3
FFAR2	Free fatty acid receptor 2
TNF-α	Tumor necrosis factor-α
FAS	Fatty acid synthase
PPAR-α	Peroxisome proliferator-activated receptor α
IL-10	Interleukin 10
ncRNA	Noncoding RNA
DNMT1	DNA methyltransferases 1
MBD2	Methyl CpG-binding structural domain protein 2
Pgc-1α	Peroxisome proliferator-activated receptor γ coactivator 1
Atgl	Adipose triglyceride lipase
Foxp3	Forkhead box p3
HATs	Histone acetyltransferases
WAT	White adipose tissue
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
MCD	Methionine- and choline-deficient
ANGPTL4	Angiopoietin-like protein 4
SP	Seabuckthorn polysaccharide
FOSs	Fructo-oligosaccharides
HFS	High-fat/high-sugar
OLA	Olanzapine
FTA	Forsythiaside A
PHI	Phillygenin
ECD	Erchen decoction
SJP	Sheng-Jiang Powder
FASN	Fatty acid synthase

LDL-C Low-density lipoprotein cholesterol
LDLR LDL receptor

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