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Impact of High-Fat Diet on Obesity-Related Diseases: The Role of Gut Microbiota-Derived Short-Chain Fatty Acids

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Abstract: The popularity of fast food has led to a rapid global increase in high-fat diets (HFD) recently. The prevalence of HFD has raised public concerns about metabolic health. Animal studies and clinical trials have implied the alternations of gut microbiota components when HFD, thereby influencing their metabolites abundances, specifically short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, which play important roles in host physiological activities. Alternations in intestinal flora abundance and components may also exacerbate gut permeability, potentially initiating inflammation which is a start of various chronic diseases. This review primarily explores mechanisms by which HFD induces obesity-related diseases, including metabolic dysfunction-associated steatotic liver disease, atherosclerosis, and type 2 diabetes mellitus. Additionally, this review demonstrates the role and effectiveness of intestinal flora, especially probiotics, and their derived SCFAs in preventing disease progression and promoting tissue regeneration in HFD-induced disorders. An intensive study on the significance of intestinal flora and their derived SCFAs to disease progression and therapeutic targets can help supplement the loop between microbial and host homeostasis.

Keywords: high-fat diet, intestinal flora, probiotics, short-chain fatty acids, obesity-related diseases.

1. Introduction

Gut microbiota has evolved along with the hosts and is an inseparable "organ" of the human body for their significant impacts on the physiological activities of the host, including biological barrier, promotion of digestion and nutrient absorption, and immune-related effects [1,2]. The human intestinal flora consists of trillions of microbial cells and thousand types of bacteria and is fairly resilient to intestinal environmental changes. The diversity of intestinal flora increases with age and is relevant to dietary structure [3,4]. Gut microbiota composition tends to stabilize between the ages of one to three years old and remains in dynamic equilibrium until in elderly individuals when a significant diminution in Bifidobacteria and a raise in Clostridium and Bacteroidetes occurs [5,6].

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Dietary composition profoundly affects the component of the intestinal flora, and it is well known that the intestinal flora may have a notable impact on host health and disease development [4,7].

In recent years, there has been a worldwide shift in the direction of high-fat diets (HFD), obesity disorders, and metabolic problems. A HFD is characterized by at least 35% of total calories coming from fats, including both unsaturated and saturated types, this diet includes a variety of foods such as animal fat, plant-derived oils, and commonly consumed processed foods [8]. HFD is particularly prevalent in Western countries, particularly the United States and European nations. Developing countries and middle-income groups are adopting HFD progressively due to quick financial growth, and demographic groups such as ladies of reproductive age and metropolitan young people are substantially impacted by these nutritional changes [9]. However, as the HFD trend becomes more popular in the world, it raises significant public health concerns. A HFD can disrupt gut microbiota composition, leading to reduced butyrate levels, which in turn can exacerbate insulin resistance and systemic inflammation [10]. A HFD can lead to liver triglyceride deposition (steatosis), causing metabolic stress, inflammation, and contributing to various metabolic disorders and liver damage, including diabetes [10]. Disruptions or imbalances in the gut microbiota caused by HFD may lead to inflammation, altered metabolism, and increased gut permeability, contributing to chronic gastrointestinal diseases like type 2 diabetes mellitus (T2DM), obesity, and inflammatory bowel disease [11].

The gut microbiota largely puts in physiological functions through metabolites, such as the short-chain fatty acids (SCFAs) created via the fermentation of dietary fibers, and SCFAs, particularly acetate, propionate, and butyrate, are anticipated to have profound results on the host metabolic health. Alterations in SCFAs production are connected to metabolic disturbances observed in obesity and T2DM. Elements causing excessive weight include energy harvest, fat storage space, and systemic inflammation, which cause modifications in digestive tract microbiota make-up [12]. In addition, the altered gut environment may exacerbate swelling and lower the manufacturing of helpful substances, speeding up the illness progression [13]. Digestive tract microbiota and their derived SCFAs are potential targets for illness development and possible treatment; the mechanisms for exactly how SCFAs manage metabolism and inflammation have not been totally elucidated. In this review, the pathological mechanisms associated with SCFAs under HFD and the therapeutic potential of SCFAs on obesity-related illnesses, such as metabolic dysfunction-associated steatotic liver disease (MASLD), atherosclerosis, and insulin resistance and type 2 diabetes, will be discussed (see Table 1).

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2. Method

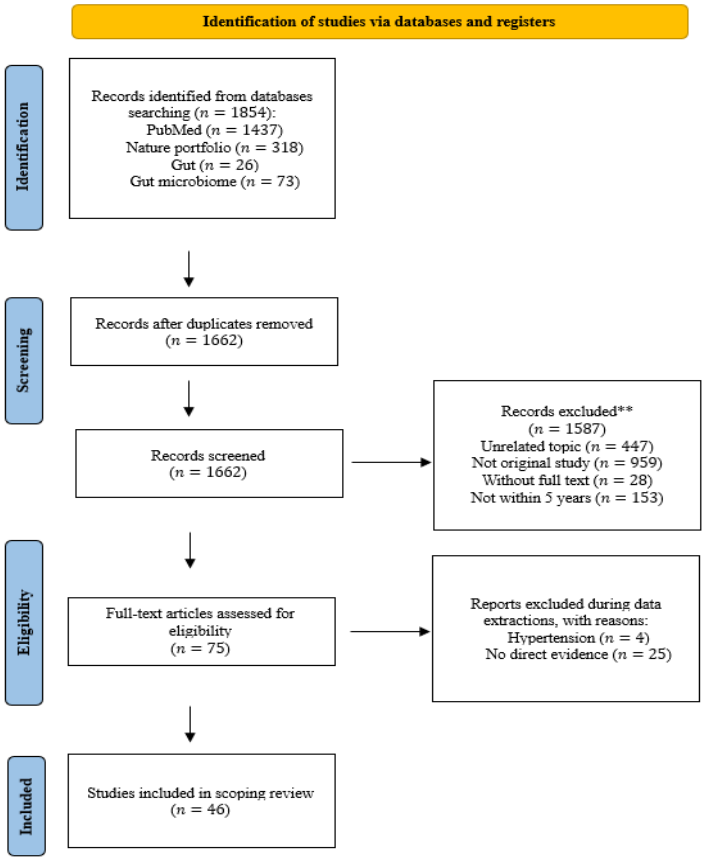

Figure 1: The PRISMA flow diagram of the searching process for the systematic review

In Figure 1, this systematic review followed PRISMA guidelines to maintain a high standard of searching, screening, and related studies. To identify studies, a complete search was conducted across multiple databases, including PubMed, Nature Portfolio, Gut, and Gut Microbiome. After removing duplicates, 1,662 records were left as unique records for screening. 75 records were identified as potentially relevant and were moved to full-text review, the full text of these 75 articles was assessed against specific inclusion and exclusion criteria. In the end, 46 articles satisfied all the inclusion and criteria and were included in this review.

3. SCFAs in MASLD

The gut microbiota plays a considerable role in the development of MASLD. Dysregulation of the gut microbiota caused by HFD has been related to altered bile acid metabolic rate, where a boost in secondary bile acids exacerbates hepatic inflammation and fat accumulation, thereby driving the progression of MAFLD toward extra-serious liver problems, including steatohepatitis and hepatocellular carcinoma (HCC) [14]. Additionally, gut-derived metabolites involving lipopolysaccharides (LPS) and trimethylamine-N-oxide (TMAO) further intensified inflammatory responses and insulin resistance, attaching dysbiosis of gut microbiota to the progression of metabolic disorders and related conditions [14]. HFD leads to a decrease in advantageous bacteria like Bifidobacterium and Akkermansia while promoting the growth of harmful bacteria such as Desulfovibrio and Anaerotruncus [15]. Introducing gut microbiota from HFD-fed mice into germ-

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free mice may directly induce hepatic lipid accumulation, inflammation, and enhanced liver cell proliferation.

NaBu, SCFAs derived from gut microbiota, transitioned macrophages from a pro-inflammatory state to an anti-inflammatory state and inhibited histone deacetylase 3 (HDAC3), which may lead to increased acetylation of the nuclear factor kappa B (NF-κB) subunit p65 and reduced liver inflammation [16]. Acetic acid generated by *Desulfovibrio vulgaris* decreased fatty acid uptake by downregulating the expression of the fatty acid transporter CD36 and promoting fatty acid β-oxidation, which may help enhance the breakdown and utilization of fatty acids and thereby reduce fat accumulation in the liver [14]. Acetate produced by *B. pseudolongum* bound to the GPR43 receptor on hepatocytes, suppressing the IL-6/JAK1/STAT3 signaling pathway, which may encourage diminution of liver cancer cell proliferation and apoptosis induction and prevent the progression of MASLD to HCC [17].

In recent years, many studies have conducted detailed research on the treatment of MASLD. For instance, partially hydrolyzed guar gum (PHGG) increased the abundance of beneficial bacteria by altering the gut microbiota composition, which produces SCFAs to maintain intestinal barrier integrity and reduce liver inflammation for MASLD patients [18]. Dietary interventions and specific microbiome-targeted therapies have been highlighted for potential management in MASLD. The Firmicutes/Bacteroidetes ratio was reduced, while beneficial bacteria like *Akkermansia* was increased under crataegus pinnatifida polysaccharide (CPP) treatment. By targeting the gut microbiota, CPP downregulated fatty acid synthesis and upregulated fatty acid oxidation pathways to reduce lipid accumulation in the liver [19].

4. SCFAs in atherosclerosis

The relationship between HFD and cardiovascular health has been thoroughly studied. Researchers focused on the interplay of gut microbiota and their SCFAs metabolites with atherosclerosis. Researchers treated SCFAs reconstruction as therapeutic targets, providing insights into the potential treatment of SCFAs on HFD-induced cardiovascular diseases. Gut microbiome and the correlated fecal SCFAs concentration differ apparently between obese and non-obese individuals [20]. HFD leads to gut dysbiosis and diminishes the presence of SCFAs-producing microbiota, including Alistipes, Bacteroides, and Clostridium, which are known to help mitigate atherosclerosis [20]. Ginger essential oil (GEO) treatment inhibited atherosclerosis progression and plasma inflammatory cytokines by modulating gut microbiota diversity [21]. A healthy microbiome increased after GEO was treated on ApoE-/- mice containing Akkermansia and Romboutsia, which are positively correlated with aortic lesions. PSRC1 deficiency under HFD enhanced TMAO production through gut microbiota dysbiosis, lipid plaque deposition, and macrophage accumulation and then accelerated atherosclerosis in ApoE-/- mice [22].

With the knowledge of the complex relationship between gut microbiota and cardiovascular disease development, bacterium alternation and SCFAs decline may be potential targets for hindering atherosclerosis progression. Paeonol (Pae) treatment on ApoE-/- mice fed with HFD regulated gut microbiota composition and increased the SCFAs production in feces, which exhibited anti-atherosclerosis efficacy [23]. Treg/Th17 balance in the spleen was subsequently restored owing to the increased SCFAs production. Butyrate prevented endothelial dysfunction in atherosclerosis on HFD-fed ApoE-/- mice against the production of reactive oxygen species (ROS) induced by IL-1β and NADPH oxidase 2 (NOX2) elevation [24]. Propionate increased IL-10 expression within the intestinal microenvironment, which in turn inhibited Niemann-Pick C1-like 1 (Npc1l1), an intestinal cholesterol transporter expression, limiting cholesterol absorption and relieving atherosclerosis in the intestine in HFD-inserted ApoE-/- mice [25]. A randomized, placebo-controlled study on humans

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with a double-blind design was further conducted, and LDL level was significantly reduced after oral propionate supplementation in individuals with high baseline LDL cholesterol levels [25].

5. SCFAs in HFD-induced obesity and type 2 diabetes mellitus

T2DM is a prevalent metabolic disorder identified with insulin resistance, disabled pancreatic β-cell, and high blood sugar levels. A HFD significantly altered the gut microbiota composition, increasing the abundance of Firmicutes while reducing the enrichment of Bacteroidetes and enhancing the ratio of Ruminococcaceae and Erysipelotrichaceae in streptozotocin-induced T2DM mice. The dysbiosis led to elevated pathways related to lipid metabolism and xenobiotic biodegradation and worsened metabolic conditions, including higher fasting blood glucose levels and rising body weight [26]. HFD elevates the permeability of intestines by reducing the expressions of tight junction proteins such as ZO-1 and occludin while targeting the gut microbiota can potentially restore intestinal integrity [27]. The function of gut microbiota in the relationship between HFD and diabetes has been highlighted. Antibiotic treatments were utilized for alternation in composition of gut microbiota and reduction in metabolic endotoxemia in HFD mice, exhibiting the depression of LPS in circulating blood, improved tolerance to blood glucose, reduced weight gain, decreased fat mass, and lessened inflammation and oxidative stress in visceral adipose tissues [27].

SCFAs are relevant to the treatment of HFD-induced obesity and T2DM. Sodium butyrate (HSB) supplement in HFD on C57BL/6J mice lower body weight gain and hepatic triglyceride deposition with decreased levels of pro-inflammation cytokines (IL-6 and TNF-α) and serum LPS concentration [28]. The extra supplementation of HSB reduced the ratio of Firmicutes to Bacteroidetes, which were elevated in HFD, thereby enhancing the balance of microbiota living in guts and epithelial barrier integrity and potentially preventing diabetes. SCFAs intake upregulated the expression of adiponectin and resistin [29], which are key adipokines related to obesity [30]. Dietary extra intake of either acetate, propionate, butyrate or mixed composition strikingly increased the amount of mRNA of adiponectin and resistin and reversed the increased CpG methylation that occurs in the promoters of adiponectin and resistin which are caused by the HFD in mice [29]. Additionally, supplementation with certain dietary components in HFD may contribute to weight management and potentially prevent diabetes [31]. Betaine supplementation in HFD mice significantly reduced the increases of body weight and simultaneously increased the abundance of Akkermansia muciniphila, which plays a significant role in maintaining a healthy mucosal microbiota network [31,32]. A study conducted on male Sprague-Dawley rats demonstrated that supplementation with 1-kestose (KES) is a viable method for regulating blood glucose levels; similar results were also shown in obese human participants who received dietary KES, possibly due to alterations in microbiota composition [33].

Table 1: Research on HFD-related diseases targeting gut microbiota and SCFAs

Disease	Animal	Treatment	Gut microbiota	SCFA	Application	Ref
NAFLD	Male C57BL/6 J	*Astragalus* polysaccharides	*Desulfovibrio vulgaris*	Acetate	Attenuate hepatic steatosis and modulate on hepatic lipids metabolism	[14]
	Male C57BL/6 J	Restricted prebiotic feeding during active phase	*Lachnospiraceae*, *Bifidobacterium*, *Lachnospiraceae*	Total	Improve hepatic steatosis, reduce serum cholesterol and increase cecal propionate production	[15]
	Male C57BL/6 J	Partially hydrolyzed guar gum	–	Total	Increase the abundance of cecal SCFAs-produced bacterium and the levels of SCFAs in the cecal samples	[18]
	Male C57BL/6 J	*Crataegus pinnatifida* polysaccharide	–	Total	Reverse disturbances in intestinal microbiota composition and elevated levels of total SCFAs	[19]

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Table 1: (continued)

NASH	Male C57BL/6 J	Sodium butyrate	_	Butyrate	Potent anti-inflammatory effect: prevent inflammatory macrophage recruitment, quelle LPS-mediated catabolism and phagocytosis of macrophages	[16]
NAFLD-HCC	C57BL/6	_	*Bifidobacterium pseudolongum*	Acetate	Suppress cell proliferation, inhibit the G1/S phase transition and induce apoptosis in NAFLD-HCC cells	[17]
Cardiovascular disease	*ApoE*$^{-/-}$ mice	Ginger essential oil	*Akkermansia* and *Romboutsia*	_	Modulate gut microbiota, inhibit the TMAO formation, reduce pro-inflammatory cytokine levels, and improve insulin resistance	[21]
Atherosclerosis	*ApoE*$^{-/-}$ mice	Sodium butyrate	_	Butyrate	Rescue the impaired endothelium-dependent relaxations and prevent endothelial dysfunction in atherosclerosis	[24]
HFD-induced obesity	*ApoE*$^{-/-}$ mice	Paeonol	*Clostridia*, *Clostridium IV*, *Lachnospiraceae*, and *Lactobacillus*	Caecum SCFAs	Restrict atherosclerosis development and collagen deposition, improve the Treg/Th17 balance	[23]
	ApoE$^{-/-}$ mice and human	Microbiota-derived metabolite propionic acid	_	Propionate	Reduces blood total and LDL cholesterol levels, suppress Npc1l1 expression and reduce intestinal cholesterol absorption	[25]
	PSRC1$^{-/-}$-*ApoE*$^{-/-}$ mice	Fecal suspension	*Desulfovibrio desulfuricans, Desulfovibrio alaskensis* and *Clostridium asparagiforme*		PSRC1 regulate TMAO generation via manipulating the gut microbiome	[22]
	Male C57BL/6 J	Sodium butyrate	_	Butyrate	Change gut microbiota composition induced by HFD and improve gut barrier, leading to lower serum LPS concentrations	[28]
	Male C57BL/6 J	Supplementation of dietary SCFAs	_	Total	Reverse the diminished adiponectin and resistin in the adipose tissue	[29]
	Kunming female mice	Supplementation with betaine	*Akkermansia muciniphila, Lactobacillus*, *Bifidobacterium*	Acetate and butyrate	Improve obesity and related metabolic syndrome through miR-378a/YY1 adjusting shaft derived from the gut microbiota	[31]
T2DM	Male SD rats and human	Supplementation of 1-kestose	*Bifidobacterium*	_	Suppress hyperinsulinemia, reduce fasting serum insulin level	[33]

6. Discussion

The complicated interactivity between gut microbiota and host metabolism, forming an "axis" between the gut and other organs, regulates metabolic processes and impacts disease occurrence. The differences in abundance and components of gut bacterium between hepatitis patients and healthy individuals indicate a correlation between microbiota and hepatitis progression [34,35]. Alternations in the component of the bacterium and the following byproducts may reflect on liver function since there are direct blood vessels and lymphatic connections between them [36]. A SCFAs-based prodrug was designed to rescue the poor pharmacokinetics of SCFAs in NASH and consequently alleviate the fibrotic liver [37]. SCFAs participate in the regulation of glucagon-like peptide-1 secreted by enteroendocrine L-cells [38], while butyrate particularly takes part in the regulation of insulin secretion from pancreatic β cells [39], which collectively indicates that gut microbiota and their derived SCFAs constitute critical links of the endocrine system of the intestine and pancreas. SCFAs

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have been shown to inhibit HDAC [40] and NF-κB [41] and activate certain G-protein coupled receptors (GPCRs) [42], triggering anti-inflammatory responses that are beneficial for cardiovascular regeneration. Thus, the inequality of intestinal flora and their derived SCFAs contributes to key therapeutic factors for organ injury not limited to the intestine.

Exogenous intake of diverse bacterial populations contributes to host health regulation. Namely, probiotics assist in maintaining healthy gut homeostasis [43]. A double blinded placebo-controlled randomized study of T2DM patients, combined berberine treatment with multi-strain probiotic products which have appeared to ameliorate dyslipidemia [44]. With the additional introduction of the Bifidobacterium breve, a better control on lipidemia (Better control of lipidemia) and cardiovascular disease risk in T2DM were achieved in the group treated with berberine and probiotic products, which together exert a hypolipidemic effect. Polygonatum sibiricum saponin (PSS) combined with probiotics was regarded as a dietary supplement for α-amylase inhibition of T2DM, accompanied by gut microbiome regulation and metabolic capacity enhancement [45]. Quinn-Bohmann, et al. reported a microbial community-scale metabolic model (MCMM) for the prediction of SCFAs production. MCMM give it a chance to visualize the impact on SCFAs production when input of different dietary, prebiotic and probiotic and individual health can be evaluated comprehensively by the combination of SCFAs production rates and blood-based biomarkers [46]. Then MCMM was utilized in the design of personalized precision interventions to optimize SCFAs production.

With the strong interaction between the gut and other organs, gut microbiota and its derived metabolites have been regarded as potential therapeutic targets for metabolic disorders. Herein, this work makes it a key point the intestinal flora-derived SCFAs with their anti-inflammation and therapeutic efficacy on obesity-related diseases. In this review, most of the articles involved were conducted through animal experiments and comparison between them is hard to conduct without an existence of SCFAs usage standards in vivo. Treatment for recovery of gut microbiota and SCFAs production has been applied in clinical trials for their key role in rebuilding metabolic homeostasis. In clinical trials involved, there is a lack on patients tracking after the treatment, making it challenge of assessing the long-term impact of SCFAs. With these limitations, the role of SCFAs in multi-organ interaction still requires further research. The adjuvant therapy of probiotics may be promoted from clinical practice to daily diet for early intervention for individuals with a high risk of metabolic disorder.

7. Conclusion

Overall, this review suggests that a HFD may induce alternations in consumption of gut microbiota and correspondingly may cause dysbiosis of metabolic products, exacerbating the occurrence of host metabolism-related diseases and upregulating inflammation levels. Providing exogenous SCFAs or treatments targeting microbial communities and their metabolites effectively restores the balance of microbial communities and their metabolites, thereby improving host metabolic abnormalities and reducing inflammation levels. This research provides a theoretical framework to explain the mechanisms behind the vicious cycle of "dysbiosis metabolic, inflammation and disease occurrence".

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