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Short-Chain Fatty Acids-A Healthy Bus between Gut Microbiota and Organs beyond the Gut

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Abstract

The impact of the gut microbiota is not limited to the intestine, but its interaction with the host produces active metabolites, which can be transported by the blood circulation to play important roles in various parts of the body. Among them, short-chain fatty acids (SCFAs), as important active products of gut bacteria, have been shown to exert anti-inflammatory and immunomodulatory effects and can play active roles as signaling molecules in the development of various intestinal and extraintestinal diseases, such as inflammatory bowel disease, colon cancer, multiple sclerosis, hypertension, allergic airway disease, obesity, diabetes, kidney disease, rheumatoid arthritis, etc. In this way, modulation of the intestinal microbiota and metabolism-active substances has gradually become a popular therapeutic method for many diseases of organs beyond the gut. To find new therapeutic targets for major human health problems, this article reviews the research on SCFAs in extraintestinal diseases.

Keywords

Short-Chain Fatty Acids, Gut Microbiota, Extraintestinal Organs, Immune Regulation, Diet

1. Introduction

A diverse range of bacteria, fungi, and viruses live in the human gut, collectively known as the gut microbiota [1] [2]. Hosts benefit from multiple powerful functions provided by microorganisms, such as digesting dietary nutrients, maintaining intestinal barrier function, and regulating the immune inflammatory system [3] [4] [5]. Gut microbiota co-exist, co-evolve with their hosts and co-maintain the dynamic balance of each other [6]. Despite its significant impact

on human health and the development of diseases, our gut microbiota has not been the focus of research until the past 20 years. In recent years, according to more and more studies, the intestinal microbiota has influenced the health of the human gut and organs beyond the gut through the production of bioactive metabolites, such as SCFAs [7] [8] [9] [10].

SCFAs are active metabolites produced by anaerobic microorganisms fermenting dietary fiber in the gut, mainly referring to fatty acids with carbon numbers between 2 and 6, such as acetate, propionate, butyrate, valerate, etc. [11] [12]. SCFAs are up taken by colonic cells via monocarboxylate transporters [13] [14], and most of them are used as energy substrates for supplying colonic cells [15]. The remaining small amount of them are transported through the bloodstream to various extraintestinal organs to act as signaling molecules through two major signaling pathways [13] [16] [17]: G protein-coupled receptors (GPCRs) and histone deacetylases (HDACs). Relying on its anti-inflammatory immunomodulatory effects, it plays a crucial role in neurological, cardiovascular, endocrine and other systems [18] [19].

SCFAs have been studied extensively in the context of intestinal and extraintestinal diseases, with the common mechanisms, anti-inflammatory and immunomodulatory effects. In this review, we summarize the beneficial effects of SCFAs on extraintestinal organs (**Figure 1**) and highlight the important value of dietary interventions to supplement probiotics and SCFAs in the treatment of

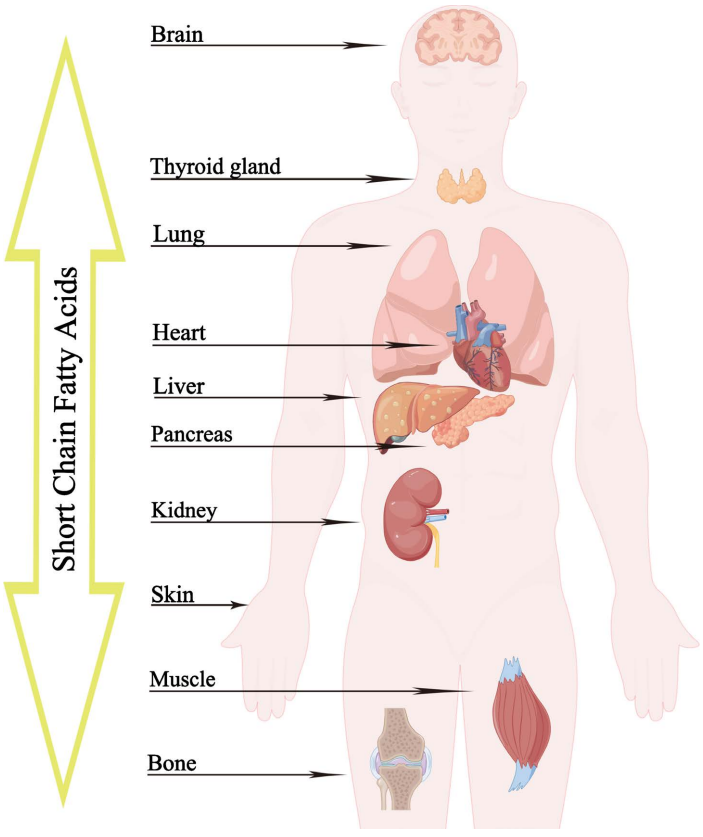

Figure 1. Association between short-chain fatty acids (SCFAs) and organs beyond the gut.

extraintestinal diseases. We aim to find new therapeutic strategies for diseases of organs beyond the gut.

2. Short-Chain Fatty Acids and Related Receptors and Epigenetic Regulation

SCFAs act as signaling molecules, which recognize and bind to G protein-coupled receptors on the cells surface or directly inhibit the activity of histone deacetylases after entering the cells. And then, they regulate gene expression and alter cell functions.

2.1. G Protein-Coupled Receptors

The G protein-coupled receptors (GPCRs) are a family of protein receptors with seven transmembrane structural domains that regulate almost all physiological functions [20]. When GPCRs recognize and bind to ligands, they can activate or inhibit downstream effectors via heterotrimeric G proteins, such as enzymes that produce second messengers or ion channels [21]. The identified G protein-coupled receptors for SCFAs include GPR40 (FFAR1), GPR41 (FFAR3), GPR43 (FFAR2), GPR120 (FFAR4), GPR84, GPR109a and Olfr78 [13] [22] [23]. These receptors are expressed in intestinal epithelial cells, immune cells, pancreatic islet cells, vascular endothelial cells, and adipose tissue. In turn, they play significant roles in maintaining the intestinal epithelial barrier, inflammatory immune regulation, stabilizing blood pressure, regulating blood glucose, and lipid metabolism. Among them, GPR41 and GPR43 are the two most prominent receptors.

2.2. Histone Deacetylases (HDACs)

Histone deacetylases (HDACs) is a protease that modifies chromosome structure and regulates gene expression at the cellular level [13]. In the nucleus, a dynamic balance between histone acetylation and deacetylation is maintained by both histone acetyltransferase (HAT) and histone deacetylases (HDACs). HAT transfers acetyl groups of acetyl coenzyme A to histone residues, thereby promoting gene expression. In contrast, HDACs deacetylates histones, coiling up chromatin and inhibiting gene transcription. SCFAs enter the cell directly through a transport channel in the cell membrane and act as a natural inhibitor of HDACs for its epigenetic regulation [24].

3. SCFAs and Nervous System

Neuropsychiatric disorders are serious threats to human health and affect the quality of life. However, at present, the treatment of these diseases mainly relies on medications to regulate neurotransmitters, and the treatment effect is not improved. In recent years, the development of the microbiota-gut-brain axis concept has attracted the interest of researchers worldwide. There is growing evidence that receptors of SCFAs exist in the central nervous system (CNS) and SCFAs enter the brain through the blood-brain barrier (BBB) [25]. They act as

signaling molecules that bind to their receptors and exert its anti-inflammatory and immunomodulatory effects, affecting brain functions [25] [26] [27]. This will be a new treatment method for neuropsychiatric diseases.

3.1. Multiple Sclerosis

Multiple sclerosis (MS) is a common immunoinflammatory neurological disorder. The main pathogenesis is that the peripherally activated self-reactive lymphocytes cross the blood-brain barrier (BBB) and secrete pro-inflammatory cytokines in response to myelin antigens in the central nervous system. Duscha *et al.* found by comparative investigation that propionic acid (PA) significantly reduced in stool and serum, Th17 and Th1 cells significantly increased in blood, and Treg cell numbers significantly reduced in MS patients compared to health controls, and after 14 days of PA supplementation, Treg numbers significantly increased and Th17 and Th1 cells reduced [27]. This suggests that PA can serve as a potent immunomodulatory supplement to multiple sclerosis drugs. In addition, three animal studies based on Experimental Autoimmune Encephalomyelitis (EAE) models found that [28] [29] [30], SCFAs suppress inflammation by altering T cell differentiation, increasing anti-inflammatory Tregs cell and decreasing pro-inflammatory T cells (Th1 and Th17), which can improve the symptoms of EAE. In addition, through a study about a mouse model of thapsigarginone-induced demyelination, Chen *et al.* [31] have shown that butyrate treatment can inhibit demyelination, enhance remyelination, promote oligodendrocyte differentiation and attenuate EAE disease progression. Overall, all these studies suggest that SCFAs can be used as possible agents to improve multiple sclerosis, but there are few studies that specifically address the role of gut derived SCFAs in human multiple sclerosis patients.

3.2. Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative amyloid disease. PD patients often present with gastrointestinal symptoms [32] [33], with pathological features typical of PD in the enteric nervous system (ENS) — overexpression of *α*Syn [34] [35]. Patients with Parkinson's disease exhibit unique changes in their gut microbiota. In several studies, the composition of the intestinal microbiota of Parkinson's patients was compared with that of healthy controls, which have found significant variations in alpha diversity and/or beta diversity in patients with Parkinson's disease [36] [37]. In addition, Unger *et al.* found a significant decrease in butyrate, acetate and propionate in the stools of PD patients, as well as a significant reduction in short-chain fatty acids (SCFAs)-producing bacteria [38]. It is thought that a decrease in SCFAs may induce changes in ENS and lead to gastrointestinal disorders in PD [38]. A PD mouse model test (induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)) demonstrated that Sodium butyrate (NaB) significantly improved neurobehavioral deficits in PD mice by enhancing intestinal endogenous glucagon-like peptide-1 (GLP-1) and acti-

vating brain GLP-1R, suggesting that NaB treatment can prevent MPTP-induced dopaminergic neuronal degeneration in mice and is a potential therapeutic target [39]. All the above studies suggest that regulating gut flora through dietary intervention can possibly be a safe treatment for PD patients.

3.3. Schizophrenia

Schizophrenia is a psychiatric disorder in which the underlying mechanisms of pathogenesis are not fully unclear. Recently, the gut-microbiota-brain axis has become a major topic of psychiatric interest. Li *et al.* found that patients with schizophrenia had significantly increased serum butyric acid levels and significantly decreased positive and negative symptom scale (PANSS) total and subscale scores after 24 weeks of risperidone treatment. There was a positive association between baseline serum levels of butyric acid and the rate of decrease in PANSS total and subscale scores, suggesting that elevated serum butyric acid levels may be associated with good treatment results in schizophrenia [40]. Therefore, modulating the gut microbiota can be used as a vital treatment for schizophrenia.

3.4. Depression

In mental disorders, depression is quite common, and it seriously impairs patients' standard of living [41]. Current antidepressants produce complete remission in no more than half of major depression disorder (MDD) patients, and new targets are urgently needed and identified to improve treatment [42]. For many years, it was thought that human immune system played a vital role in depression disorder [43]. As important immunomodulators, SCFAs are emerging as new treatments for depression. Studies have found that transplanting feces from patients with major depressive disorder (MDD) into germ-free animals leads to behavioral and physical features of depression [44]. The results of an animal experiment showed that the three main SCFAs (acetic acid, propionic acid and valeric acid) were significantly reduced in depressed mice compared to control mice [45]. In addition, Bettina *et al.* analyzed fecal SCFAs from depressed patients and found a negative correlation between depressive symptoms and butyrate and propionate levels [46]. The above study further confirmed the strong association between short-chain fatty acids and depressive symptoms. Although the exact molecular mechanism is unknown, the gut microbiota plays an important role as a "mental probiotic" in alleviating depressive symptoms.

4. SCFAs and Cardiovascular System

Increasing morbidity and mortality from cardiovascular disease (CVD) pose a health threat and economic burden to our society. This forces us to actively search for more effective strategies to prevent and treat CVD. In recent years, there has been a strong passion on the interactions among the human gut microbiota, its metabolites SCFAs and cardiovascular disease. Treatment of cardiovascular disease with manipulation of the gut microbiota and active metabolites

may prove to be an effective strategy.

4.1. Hypertension and Atherosclerosis

Hypertension is an independent and preventable risk factor for the development of cardiovascular disease, often coexisting with and accelerating the progression of atherosclerosis, posing a serious threat to human health. In recent years, there has been increasing interest in the role of gut microbes in hypertension and atherosclerosis and their potential mechanisms. According to several studies, gut microbiota imbalances may contribute to hypertension and cardiovascular injury [47] [48] [49], this may be related to intestinal epithelial barrier dysfunction and the resulting activation of inflammatory cells and production of pro-inflammatory cytokines [50] [51]. Evidence suggests that SCFAs keep the intestinal barrier and modulates intestinal immune cells to enhance intestinal immune function [52]. In turn, they prevented the development of hypertension and atherosclerosis and slowed their progression. In addition, SCFAs (propionate and butyrate) reduced the production of pro-inflammatory factors such as TNF-*α*and NO by LPS-stimulated neutrophils by inhibiting nuclear factor kappa B (NF-κB) activity and histone deacetylase (HDAC) [51] [53]. It exerts its anti-inflammatory effects and attenuates cardiovascular damage in hypertension. Another study demonstrated that SCFAs can be involved in the regulation of blood pressure through G olfactory receptor 78 (Olfr78) and G protein receptor 41 (Gpr41) expressed in vascular or renal tissues [54] [55]. The above studies provide further experimental evidence for the importance of microbiota derived SCFAs in promoting cardiovascular health in hosts, suggesting that SCFAs supplementation treatment can prevent hypertension and reduce atherosclerosis and cardiac damage, and is a new approach to prevent hypertension and cardiovascular damage.

4.2. Heart Failure

Heart failure is a result of imbalance in cardiac function due to various primary heart diseases [56]. Currently, more and more studies are confirming the "intestinal hypothesis of heart failure", in which patients with heart failure have impaired intestinal barrier function, leading to bacterial translocation and increased levels of pro-inflammatory cytokines in the blood [57] [58] [59]. Recent data show that SCFAs can maintain the integrity of the intestinal epithelial barrier and reduce bacterial translocation [52]. This prevents the development of heart failure. An animal study showed that SCFAs can bypass carnitine palmitoyltransferase 1 (CPT1) to support energy production in the failing heart and improve cardiac energy failure in the presence of reduced CPT1 activity on the outer mitochondrial membrane [60].

4.3. Arrhythmias

Arrhythmias are intractable cardiovascular diseases that lead to heart failure or

sudden cardiac death. Atrial fibrillation (AF) is the most prevalent common arrhythmia worldwide, and Zuo *et al.* found an imbalance in the composition of the gut microbiota in patients with AF [61] [62] [63]. Dysregulated gut microbiota viability may contribute to AF development. There is conclusive evidence for the coexistence of inflammation and the initiation of atrial fibrillation [64] [65]. Furthermore, as HDACs inhibitor, SCFAs can prevent the intestinal barrier from being disrupted by inhibiting the LPS-NLRP3 inflammasome axis [66]. Ca2+ and GPR43-dependent mechanisms reduce NLRP3 inflammasome activation by acetate, thereby preventing inflammation-related arrhythmias [67]. It has also been shown that propionate prevents the development of myocardial infarction-induced ventricular arrhythmias (VA) and cardiac electrophysiological instability through parasympathetic activation based on the gut-brain axis [68].

5. SCFAs and Respiratory System

The gut-lung axis is becoming a new hotspot for research because of the interaction between intestinal flora and the respiratory system [69]. A growing number of studies have shown that metabolites produced by the gut microbiota, SCFAs, play an important role as immunomodulators in the development of lung diseases.

5.1. Pulmonary Infections

Microbial infections are major public health problem. Today, antibiotic resistance is increasing, and infections caused by multi-drug resistant microorganisms are becoming more common. Therefore, we need to find alternative ways to enhance host defense and control inflammation. The pulmonary immune response can be modulated by metabolites produced by the intestinal flora, such as SCFAs [70] [71]. One study found that germ-free mice were more likely to contract lung disease than mice carrying commensal bacteria [72] [73]. Patients with intestinal disease have lower SCFAs levels and are also more likely to develop lung disease [74]. According to these findings, the gut microbiota influences lung immunity. The role of SCFAs as important active intestinal metabolites in the regulation of inflammation is not limited to the gut. In fact, SCFAs can enter the bloodstream and act at distal sites, such as the lungs [16], preventing the lung infections. SCFAs can directly inhibit the growth and virulence of pathogens [75] [76] [77]. Meanwhile, short-chain fatty acids can also bind to their free fatty acid receptor 2 (FFAR2) and FFAR3, and inhibit activity of histone deacetylases (HDACs), activating a signaling cascade that regulates the host defense response [78] [79]. These results suggest that SCFAs could potentially play a therapeutic role in infection control by exploiting their anti-inflammatory biological properties.

5.2. Asthma

Eosinophils are important effector cells in allergic asthma, and in animal model

of allergic airway disease studies, mice fed SCFAs (butyrate, propionate, or acetate) exhibited lower severity than mice fed a normal diet [80]. According to another study, children with high levels of SCFAs in their stools had a lower risk of allergy to allergens and asthma later in life [81]. Many studies have further shown that butyrate and propionate limit eosinophil survival and migration through their inhibitory effects on HDACs [82]. SCFAs inhibit lymphocyte activation and presentation by Dendritic Cells (DCs), reduce IL-4-producing CD4+ T cells, and decrease immunoglobulin E (IgE) levels [80]. In addition, they can downregulate mast cell activation-related gene expression, inhibit antigen-induced mast cell degranulation and reduce the release of many inflammatory mediators (including tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6)) [83]. This reduces lung inflammation in mice with allergic airway disease. In addition, B cells are essential for the development and maintenance of allergic disorders with their antigen-presenting role [84]. Butyrate reduces AID and Blimp-1 gene expression in vivo by inhibiting histone deacetylation of specific miRNA host genes in B cells, thereby suppressing local and systemic antibody responses [85]. Therefore, increasing SCFAs levels through dietary intake can help to reduce the inflammatory response in allergic airway disease and can be a potential new therapeutic strategy to prevent over this disease.

5.3. Other Pulmonary Diseases

Researchers have shown that the gut microbiota also affects the pathophysiology of other lung diseases. Hu *et al.* characterized the microbial composition of feces from Pulmonary Tuberculosis patients and healthy controls and found the intestinal flora of TB patients is characterized by a significant reduction of bacteria producing SCFAs as well as associated metabolic pathways, suggesting that gut bacterial characteristics could potentially be used to distinguish healthy from TB patients [86]. In addition, butyric acids blocked the expression of genes associated with transforming growth factor β1 (TGF-β1)-induced fibroblast activation, exhibiting potent antifibrotic activity [87]. This is expected to be the biologic agent in the treatment of Idiopathic pulmonary fibrosis (IPF).

6. SCFAs and Endocrine System

6.1. Diabetes

Diabetes mellitus (DM) and its complications remain a major global health problem. The data suggest that SCFAs play vital roles in the pathogenesis of diabetes. For one, disruption of the intestinal barrier may promote the development of DM [88]. It has been proven that SCFAs promote intestinal epithelial cell proliferation, strengthen the tight junctions between intestinal epithelial cells, and regulate the activity of immune cells to maintain and strengthen the physical, chemical, and immune barriers of the gut [52]. Thereby SCFAs can indirectly protect pancreatic β-cells from autoimmune damage. In addition, it was found that FFAR2 was expressed in pancreatic β-cells [89], suggesting that

SCFAs may also directly regulate the proliferation and differentiation of pancreatic β-cells through FFAR2. Second, insulin resistance is also an important pathogenesis of DM [90]. The receptor of SCFAs, GPR43, was expressed in liver adipocytes [91]. SCFAs can enhance insulin sensitivity of liver and adipose tissue and promote glucose uptake and glycogen synthesis to regulate blood glucose. Third, appetite regulation is also an important therapeutic approach to control blood glucose. It has been shown that SCFAs (butyrate, acetate) can stimulate enteroendocrine cells (L cells), increase the secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), and reduce food intake [92] [93] [94] [95]. It also inhibits hypothalamic AMP-activated protein kinase (AMPK) activity to increase the expression of anorexigenic neuropeptides to control appetite [96].

6.2. Graves' Disease

Graves' Disease is a typical specific autoimmune disease [97]. Recently, many studies have shown that SCFAs produced by intestinal microorganisms can regulate regulatory T (Treg) cells and T helper cells (Th17) in extraintestinal tissues and play a crucial role in the development of extraintestinal autoimmune diseases [98]. Su *et al.* found that the abundance of SCFAs-producing bacteria of GD patients was reduced and the levels of SCFAs were significantly lower, especially propionic acid. These abnormalities led to a decrease in the number of Tregs and an increase in the number of Th17 cells, resulting in immune imbalance and inflammation in GD patients. It is proposed that dysregulated flora in stool has the potential to be used as an auxiliary marker for the diagnosis of GD. It can also be used as an adjuvant treatment method [99].

7. SCFAs and Fatty Liver

The increasing incidence of fatty liver disease has been one of the major challenges for human health. Recently, more and more attention has been paid to the role of gut microbes in liver diseases, and the gut-liver axis is gradually becoming a research hotspot [100]. Intestinal barrier dysfunction leads to the promotion of pathogen-associated molecular pattern (PAMP) through portal influx into the liver, triggering a pro-inflammatory cascade response, which is an important common mechanism in the development of alcoholic fatty liver disease (AFLD) and non-alcoholic fatty liver disease (NAFLD) [100] [101]. Compelling data from many animal models suggest that short-chain fatty acids reduce steatohepatitis by maintaining intestinal barrier function, reducing bacterial translocation, modulating immune inflammation, and preventing oxidative damage to the liver [102] [103] [104] [105] [106]. In addition, SCFAs can directly reduce hepatic cholesterol and fatty acid synthesis, while increasing hepatic lipid oxidation to reduce hepatic lipid deposition and prevent the development of fatty liver [107] [108] [109]. It is important to note that non-alcoholic fatty liver disease (NAFLD) is a manifestation of the metabolic syndrome in the liver and shares common mechanisms with obesity, diabetes and cardiovascular diseases [105].

SCFAs mediate the production of satiety in the brain by stimulating secretion of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) in a GPR-dependent manner [92] [93] [94] [95], that reduce excessive fat intake and decrease the incidence of fatty liver. Another study showed that inulin alleviated inflammation in alcoholic liver disease (ALD) by suppressing M1 and promoting M2 induced by SCFAs, providing a theoretical basis for regulating intestinal flora as an inexpensive intervention for the prevention and treatment of ALD [110]. Therefore, the increase in SCFAs produced by fermentation of dietary fiber is a valuable strategy for the prevention and mitigation of fatty liver.

8. SCFAs and Muscle

Skeletal muscle is the largest organ in humans and plays a key role in whole-body energy metabolism. Evidence is growing that the human gut microbiota regulates skeletal muscle metabolism and function. The "gut-muscle axis" [111] [112] has gradually become a research hotspot in recent years. Evidence shows that mice with depleted gut microbes exhibit reduced skeletal muscle mass, and reduced muscle strength [113] [114] [115]. In contrast, probiotics supplementation increases skeletal muscle mass in obese mice [116] [117]. This regulatory interaction between gut microbes and skeletal muscle is partially mediated by short-chain fatty acids. SCFAs has been proved to affect lipid, carbohydrate, and protein metabolism in skeletal muscle tissue. And activation of AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor (PPAR), and inhibition of HDACs may be key mechanisms for these changes in skeletal muscle [118] [119] [120] [121]. Therefore, modulating the gut microbiota with dietary interventions or probiotics supplementation would be an exciting therapeutic strategy for muscle-related diseases and syndromes. Among them, sarcopenia, characterized aging-related loss of skeletal muscle mass and function, is an age-related skeletal muscle disease that affects the quality of life of the elderly and increases the incidence of disability and mortality [122] [123]. To date, exercise and nutrients have been the primary treatment for the disease, but older patients have poor adherence and cannot achieve long-term sustainability [124]. One study found that patients with sarcopenia exhibit a different fecal microbiota composition: the species producing short-chain fatty acids (SCFAs) were significantly depleted (Faecalibacterium, prausnitzii *et al.*) [125] [126]. Further studies have shown that probiotics supplementation with SCFAs (acetate, propionate and butyrate) is beneficial in maintaining muscle mass and strength and enhancing exercise endurance in germ-free mice [116] [127] [128] [129] [130].

9. SCFAs and Urinary System

In renal disease, uncontrollable inflammation, oxidative stress, and imbalance of immune response are associated with impairment of renal function [131]. Short-chain fatty acids (SCFAs) can improve renal function in acute kidney in-

jury through their anti-inflammatory properties and inhibition of oxidative stress. An animal study, using an adenine-induced mouse model of chronic kidney disease (CKD), showed that propionic acids, via FFA2 and FFA3 receptors, inhibit the expression of pro-inflammatory factors, and significantly reduce serum creatinine (Cr) and urea nitrogen levels [132]. Another study showed that the key mechanism of SCFAs against acute kidney injury (AKI) is local and systemic reduction of inflammatory cytokine and chemokine production through inhibition of LPS-TLR4-induced NF-κB and MAPK inflammatory signaling pathways, which may be related to GPCRs activation and autophagy regulation [133] [134] [135]. In addition, renal anemia is a serious complication of chronic kidney disease (CKD) and current erythropoietic and iron supplementation treatments have limitations. Recently, several relevant studies have highlighted that inflammatory status affects the progression of renal anemia in various ways [136] [137]. Gut microbiota and SCFAs can produce anti-inflammatory and immunomodulatory effects by activating regulatory cells of the immune system to improve anemia [138]. Other studies using mouse kidney transplantation models have shown that allograft rejection can be reduced by supplementing the diet with short-chain fatty acids and high fiber [139].

10. SCFAs and Skin

Psoriasis is a common immune-related inflammatory disease of the skin that severely affects human physical and mental health. Its pathogenesis is multifactorial, with the accelerated TNF-*α*/IL-23/IL-17 axis being the main pathological mechanism of psoriasis [140]. It leads to excessive proliferation and abnormal differentiation of epidermal keratinocytes. In addition, Tregs defects are also important in the pathogenesis of psoriasis [141]. Restoring Tregs activity and reducing the release of pro-inflammatory factors is emerging as a promising therapeutic target for psoriasis [142]. SCFAs can promote the activity of regulatory T cells (Tregs), which play an active role in inflammatory skin diseases. Using a mouse model of psoriasis-like skin inflammation, Luu *et al.* demonstrated that SCFAs, particularly butyrate, reduced the skin inflammatory response by restoring suppressed regulatory T cell (Tregs) activity through GRP43 as well as HDACs to upregulate IL-10 and Foxp3 transcripts and downregulate IL-17 and IL-6 [143] [144] [145]. In addition, Smith *et al.* found that in vitro and in vivo treatment of germ-free mice using propionate both significantly increased the number of Tregs and the expression of Foxp3 and IL-10 [98].

11. SCFAs and Rheumatoid Arthritis (RA)

Rheumatoid arthritis is an immune-mediated chronic joint inflammation and injury featured by bone destruction and synovial hyperplasia [146]. In contrast, SCFAs, as modulators of the immune system [146], can alleviate arthritic symptoms and are emerging as a novel treatment strategy for RA. To explore the role and preliminary mechanisms of gut microbiota derived SCFAs in RA, a study

conducted by Yao *et al.* analyzed feces samples from patients with RA and those with healthy controls.

Four SCFAs (acetate, propionate, butyrate and valerate) in stool were found to be positively correlated with regulatory B cells (Bregs) levels in peripheral blood in RA patients compared to healthy controls [147]. To investigate in depth the role of gut microbiota-derived SCFA in RA, Yao *et al.* using a collagen-induced arthritis (CIA) model, found significantly higher SCFAs levels in the stool of mice after treated with SCFAs and reduced inflammatory cell infiltration and synovial hyperplasia in the knee and ankle joint cavities of mice [147]. It was further elucidated that the therapeutic effect of SCFAs on arthritis was achieved through regulation of B-cell differentiation by the FFA2 receptor (GPR43), along with increased serum IL-10, IL-13 and TGF-β and decreased IL-6, IL-1β and TNF-α [147]. Therefore, increasing dietary fiber diet to enhance SCFAs levels may become an effective treat strategy for rheumatoid arthritis.

12. SCFAs and Tumor Immunology

There are indications that short-chain fatty acids (SCFAs) produced by gut microbes help to regulate immune cells and cytokines with anti-tumor properties. Therefore, manipulation of SCFAs in the gut by altering the microbiota structure could be a new approach for cancer prevention and treatment in a variety of extraintestinal organs [148]. Inflammatory factors and dysbiosis of the gut microbes may contribute to cancer risk in diets low in fiber, fat, and sugar [149]. A high fiber diet enhances the "healthy" microbiota and strengthens the tight junctions of the intestinal mucosa, thereby reducing the leakage of disease-causing bacteria and their carcinogenic effects, as well as limiting the proliferation of cancer cells by acting as HDACs inhibitors and stimulating cyclin-dependent kinase inhibitors [150]. Bindels *et al.* treated a mouse model with oral inulin-type fructose (ITF) and showed a reduction in cancer cell proliferation and a reduction in inflammation associated with cancer development [151]. Butyric acid also inhibits cell growth and activates programmed cell death, producing a direct inhibitory effect on cancer cells [152]. In addition, short-chain fatty acids (valerate and butyrate) enhanced the antitumor activity of cytotoxic T lymphocytes (CTL) and chimeric antigen receptor (CAR) T cells by modulating metabolism and epigenetics [153]. Butyrate and valerate were identified as having therapeutic potential in the immunotherapy of cellular carcinoma. Another study found that fecal SCFAs concentrations were associated with the efficacy of programmed cell death-1 inhibitors (PD-1i) in the treatment of solid tumors. Therefore, fecal short-chain fatty acids concentration could be used as a routine test to assess the effectiveness of PD-1i therapy [154]. These results confirm the role of gut microbiota and metabolites in controlling cancer progression. Therefore, supplementation of SCFAs in the gut by altering gut microbiota could be a new approach for cancer prevention and treatment.

13. Conclusion

Short-chain fatty acids play a central role in the diet-gut microbiota-host metabolic axis through their maintenance of the intestinal epithelial barrier, anti-inflammatory, immunomodulatory, and anti-tumor properties. As a result, short-chain fatty acids may provide an additional therapeutic target for extraintestinal diseases through altering the metabolic status of the host. How to regulate short-chain fatty acids is another hot topic of research. For example, SCFAs can be indirectly regulated through high dietary fiber diets (cereals, vegetables, and fruits), oral probiotics, fecal transplants, and targeted antimicrobial enzyme inhibitors to modulate the intestinal microbiota, as well as direct supplementation with SCFAs preparations [155]. In addition, it is recommended that short-chain fatty acids be routinely measured in feces and serum, such as glucose, glycated hemoglobin, and cholesterol levels, to more visually assess disease status, progression, and prognosis and implement more individualized therapeutic interventions. This will require the future development of convenient instrumentation to measure human gut microbes and their metabolite levels using multi-omics methods with higher taxonomic resolution. Further studies are also needed to clarify the role of various gut bacteria and SCFAs in the pathophysiology of human diseases and how they can be utilized and modulated to produce useful effects. Overall, the healthy value of deciphering, monitoring, and manipulating the SCFAs is tremendous, and that calls for the collective efforts from academic, industrial, and clinic entities.

SCFAs, as important active products of gut bacteria, can play a role as signaling molecules and exert anti-inflammatory and immunomodulatory effects on various organs beyond the gut, including brain, lung, heart, liver, pancreas, kidney, muscle, bone, etc. Modulation of the intestinal microbiota and metabolism-active substances has gradually become a popular therapeutic approach for extraintestinal diseases.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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