



Review Article

Double-side role of short chain fatty acids on host health via the gut-organ axes

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ABSTRACT

Short chain fatty acids (SCFA) exist in dietary foods and are produced by the fermentation of gut microbiota, and are considered an important element for regulating host health. Through blood circulation, SCFA produced in the gut and obtained from foods have an impact on the intestinal health as well as vital organs of the host. It has been recognized that the gut is the “vital organ” in the host. As the gut microbial metabolites, SCFA could create an “axis” connecting the gut to other organs. Therefore, the “gut-organ axes” have become a focus of research in recent years to analyze organism health. In this review, we summarized the sources, absorption properties, and the function of SCFA in both gut and other peripheral tissues (brain, kidney, liver, lung, bone and cardiovascular) in the way of “gut-organ axes”. Short chain fatty acids exert both beneficial and pathological role in gut and other organs in various ways, in which the beneficial effects are more pronounced. In addition, the beneficial effects are reflected in both preventive and therapeutic effects. More importantly, the mechanisms behinds the gut and other tissues provided insight into the function of SCFA, assisting in the development of novel preventive and therapeutic strategies for maintaining the host health.

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1. Introduction

The intestine has long been regarded as the most important organ for the human body to defend against external contaminants. The intestinal epithelium containing three different cell types (enterocytes, Paneth cells, and goblet cells), which are considered to be the first line of defense (Gao et al., 2020). Additionally, the intestinal microbiota colonizing the gut also plays a crucial role in

maintaining the health condition of healthy. Firmicutes and Bacteroidetes dominate intestinal microbiota, accounting for almost 80% of the total population (Foster and Neufeld, 2013). Links between the gut microbiota and numerous metabolic diseases, such as diabetes, obesity, and nervosa, have been reported (Fan and Pedersen, 2021).

The intestinal microbiota produces various metabolites for intestinal cells, including short-chain fatty acids (SCFA), lactate, deoxycholic acid (DCA), and tryptophan metabolites, which could exert beneficial effects on the host (Nicolas and Chang, 2019). Researchers have been particularly interested in the bioactive role that SCFA play. Short chain fatty acids could be utilized for energy by intestinal cells or released into the portal vein circulation for utilization by peripheral tissues and provide 10% of the daily caloric demand of the human body (Alexander et al., 2019). In addition, as key bacterial metabolites, SCFA could affect various organs, including brain and liver (Koh et al., 2016). Recently, the concept of “gut-organ axes” has been proposed to help create innovative

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diagnosis and therapeutic approaches (Ahlawat et al., 2021). Therefore, the present study summarized the potential effects of SCFA in human health as well as the underlying cause-effect mechanisms in theoretically based on “gut-organ axes”.

2. Exogenous intake, endogenous biosynthesis, and absorption of SCFA

To explore the impact of SCFA on the body health, we must understand the sources and absorption mechanism of SCFA firstly. There are currently limited reviews on the content of SCFA in food as most studies focus on the production of SCFA by intestinal microbiota fermentation. Therefore, we summarize the sources and absorption of SCFA in the body, especially the contents of SCFA in milk, which have not been reported systematically in the previous studies. These findings will be explained in detail in the following contents.

2.1. Biosynthesis and intake of SCFA

There are two sources from which the intestinal epithelium can obtain SCFA: one is bacterial fermentation (main source), and the other one is direct intake via food (Koh et al., 2016; Zhao et al., 2022). Short chain fatty acids are the primary fermentation by-products of non-digestible carbohydrates (NDC), which are digested by the gut microbiota in the cecum and colon after evading digestion in the small intestine. The main SCFA produced are acetate, propionate and butyrate, with acetate accounting for 60% to 70% of the total SCFA (Morrison and Preston, 2016). The acetate-producing bacteria are widely distributed, such as *Akkermansia muciniphila*, *Ruminococcus* spp. and *Bacteroides* spp. while the bacteria producing propionate (*Bacteroides* spp. and *Ruminococcus obeum* etc), and butyrate (*Coprococcus comes* and *Roseburia* spp.) are highly conserved and specific (Zeng et al., 2019). As illustrated in Fig. 1, a variety of factors, including nutrition and intestinal microbiota composition, have an impact on the biosynthesis and

quantity of SCFA. The two metabolic pathways that gut microbiota uses to produce acetate are mainly formed by hydrolysis of acetyl-CoA and Wood-Ljungdahl pathway (Ragsdale and Pierce, 2008). There are three different ways for the colonic bacteria to produce propionate, including the succinate, acrylate and propanediol pathways, where deoxyhexose sugars are used as substrates (Scott et al., 2006). There are two potential routes to produce butyrate in the gut. The first is the classical pathway, which involves butyryl-CoA being converted to butyrate via phosphor-transbutyrylase and butyrate kinase. Another pathway is the conversion of butyryl-CoA to butyrate via butyryl-CoA:acetate CoA-transferase (den Besten et al., 2013; Duncan et al., 2002). When less fermentable fiber is available, the microbes also use amino acids in the diet to produce SCFA (Wall et al., 2009). Milk, as an important human food source, contains a considerable amount of SCFA (Zhao et al., 2022). The concentrations of SCFA in milk are listed in Table 1.

2.2. SCFA absorption

The concentration of SCFA varied among different intestinal segments, with the cecum and proximal colon having the highest concentration (70–140 mM), and the distal colon having a lower concentration (20–140 mM), respectively (Sun et al., 2017). This difference results from the absorption characteristics of SCFA with various transporters. Due to their hydrophobicity, as shown in Fig. 2, SCFA could be easily absorbed through the apical membrane of colon cells via nonionic diffusion (passive diffusion) (McNabney and Henagan, 2017). In addition, H^+ -dependent monocarboxylate transporter 1 (MCT1) and sodium-coupled monocarboxylate transporters (SCMT) are also important mediators of SCFA absorption. Solute carrier family 5, member 8 (SLC5A8) is a crucial component of SCMT (Liu et al., 2018; Silva et al., 2020). Furthermore, G-protein coupled receptor (GPR) 41, GPR43 and GPR109A are the receptors, GPR41 and GPR43 later known as free fatty acid receptors (FFAR)3 and FFAR2, which could activate SCFA (Bolognini et al., 2016). Butyrate is consumed in the colon as the preferred

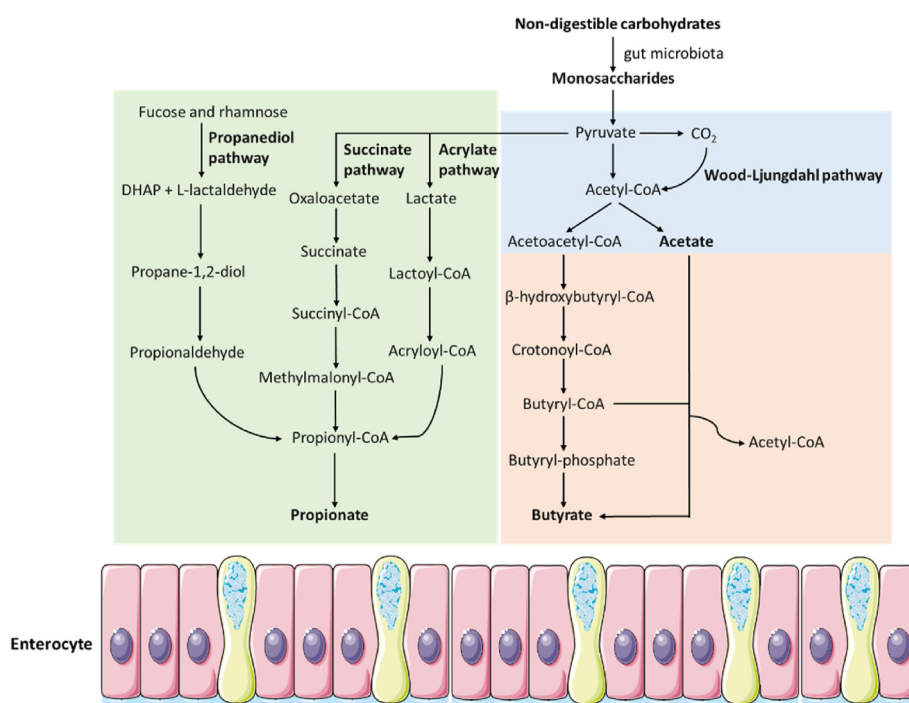


Fig. 1. The endogenous biosynthesis of short chain fatty acids. DHAP = dihydroxyacetone phosphate.

Table 1

The list of short chain fatty acid concentrations in milk.

Item	Sample	Detection method	Concentration	Unit of measure	Reference
Butyrate	Human milk collected from China (<i>n</i> = 90)	Thin-layer chromatography	0.06 ± 0.01 in Zhengzhou, 0.03 ± 0.01 in Wuhan, and 0.07 ± 0.03 in Harbin	% of triglycerides	Chen et al. (2020)
Caproate	Human milk collected from China (<i>n</i> = 90)	Thin-layer chromatography	0.01 ± 0.00 in Zhengzhou, 0.01 ± 0.00 in Wuhan, and 0.03 ± 0.01 in Harbin	% of triglycerides	Chen et al. (2020)
Butyrate	Human milk collected from China (<i>n</i> = 180)	Ultra-high-performance supercritical fluid chromatography	0.06 ± 0.06 in full-term colostrum milk, 0.07 ± 0.05 in full-term transitional milk, and 0.24 ± 0.20 in full-term mature milk	mg/g milk fat	Dai et al. (2020)
Formate	Human milk collected from Australia, Japan, Norway, South Africa, and USA (<i>n</i> = 109)	Nuclear magnetic resonance analysis	Range: 15.2–4960.3 Median: 43.7	μM	Stinson et al. (2020)
Acetate	Human milk collected from Australia, Japan, Norway, South Africa, and USA (<i>n</i> = 109)	Nuclear magnetic resonance analysis	Range: 13.5–4307.7 Median: 46.8	μM	Stinson et al. (2020)
Butyrate	Human milk collected from Australia, Japan, Norway, South Africa, and USA (<i>n</i> = 109)	Nuclear magnetic resonance analysis	Range: 4.8–409.5 Median: 95.6	μM	Stinson et al. (2020)
Butyrate	Human milk collected from United Kingdom (<i>n</i> = 102)	Gas chromatography-mass spectrometry	Range: 0–3.5	mg/100 mL	Prentice et al. (2019)
Acetate	Milk collected from Canada (<i>n</i> = 16, four replicates from each type of milk)	Liquid chromatography-tandem mass spectrometry	38.0 ± 1.0 in skim milk, 37.0 ± 1.0 in 1% milk, 46.0 ± 1.0 in 2% milk, 43.0 ± 1.0 in 3.25% milk	μM	Foroutan et al. (2019)
Propionate	Milk collected from Canada (<i>n</i> = 16, 4 replicates from each type of milk)	Liquid chromatography-tandem mass spectrometry	1.0 ± 0.1 in skim milk, 2.94 ± 0.12 in 1% milk, 2.0 ± 0.1 in 2% milk, 2.0 ± 0.1 in 3.25% milk	μM	Foroutan et al. (2019)
Butyrate/iso butyrate	Milk collected from Canada (<i>n</i> = 16, 4 replicates from each type of milk)	Liquid chromatography-tandem mass spectrometry	37.0 ± 1.0 in skim milk, 34.9 ± 10.2 in 1% milk, 24.0 ± 1.0 in 2% milk, 27.0 ± 1.0 in 3.25% milk	μM	Foroutan et al. (2019)
Valerate/iso valerate	Milk collected from Canada (<i>n</i> = 16, 4 replicates from each type of milk)	Liquid chromatography-tandem mass spectrometry	1.8 ± 0.1 in skim milk, 4.0 ± 0.2 in 1% milk, 4.18 ± 0.03 in 2% milk, 4.91 ± 0.13 in 3.25% milk	μM	Foroutan et al. (2019)
Caproate	Milk collected from Canada (<i>n</i> = 16, 4 replicates from each type of milk)	Liquid chromatography-tandem mass spectrometry	1.8 ± 0.1 in skim milk, 4.0 ± 0.2 in 1% milk, 4.18 ± 0.03 in 2% milk, 4.91 ± 0.13 in 3.25% milk	μM	Foroutan et al. (2019)
Butyrate	Milk collected from China. Human (<i>n</i> = 1), cow (<i>n</i> = 15), goat (<i>n</i> = 15), yak (<i>n</i> = 38), buffalo (<i>n</i> = 9), camel (<i>n</i> = 12)	Gas chromatography -flame ionization detection	0.10 ± 0.01 in human milk, 1.23 ± 0.02 in cow milk, 1.62 ± 0.03 in buffalo milk, 0.93 ± 0.02 in goat milk, 2.05 ± 0.03 in yak milk, and 12.2 ± 0.09 in camel milk	g/100 g total fatty acids	Teng et al. (2017)
Butyrate	Milk collected from Brasil (<i>n</i> = 12)	Gas chromatography	3.53 ± 0.95 in raw milk, 2.87 ± 0.46 in pasteurized milk, and 2.86 ± 0.40 in ultra high temperature treated milk	% total fatty acids	Pestana et al. (2015)

energy source for colon cells. Acetate and propionate subsequently enter the portal vein, while propionate is metabolized in the liver, acetate becomes the SCFA with the highest concentration in the peripheral circulation (Koh et al., 2016). The effects of SCFA on host health, including gut and other organs, are outlined in the following sections.

3. SCFA have both beneficial and pathological effects on gut health

The intestinal barrier is crucial for the body against external pollutants, which consists of physical, chemical, immunological and microbial barriers (Gao et al., 2020). On the basis of recently reported studies (Ma et al., 2022), we suggest that SCFA play a dual effect on intestinal health in these four (physical, chemical, immunological and microbial barriers) aspects.

According to a published study, intestinal development and the expression of tight junction (TJ)-related genes were both improved in the small intestine and colon of weaned piglets when acetate, propionate, and butyrate were infused into the stomach (Diao et al., 2019). An in vitro study showed that acetate, propionate, and butyrate improved the impaired intestinal TJ integrity through the AMP-activated protein kinase (AMPK) signaling pathway (Eamin et al., 2013). The findings in mice and HCT116 cells clarified that butyrate reduced intestinal permeability and enhanced the TJ-related gene level in a hypoxia-inducible factor-1 (HIF-1)-dependent manner (Fachi et al., 2019). Results from IPEC-J2 cells showed that butyrate had a favorable effect on TJ gene expression (Ma et al., 2012). Butyrate exposure at 0.5 to 2.5 mM boosted the expression of zonula occludens-1 (ZO-1) and occludin in the IPEC-J2 cells, but not at the concentration of 5 mM (Saleri et al., 2022). However, there was no discernible variation in mRNA levels of ZO-1 and occludin when Caco-2 cells were exposed to acetate, propionate, and

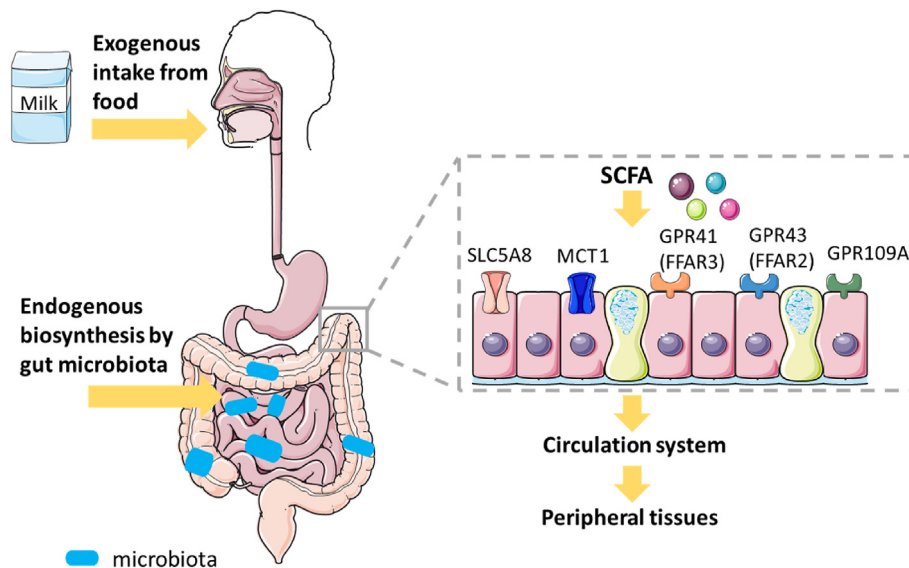


Fig. 2. The sources and absorption of SCFA. The sources of SCFA in body includes exogenous intake from food, such as milk, and endogenous biosynthesis of non-digestible carbohydrates by gut microbiota in the cecum and colon. The transporters including SLC5A8, MCT1 and the receptors including GPR41 (FFAR3), GPR43 (FFAR2), and GPR109A are involved in the absorption of SCFA in the intestine. The absorbed SCFA enter the portal vein, and then dispersed to peripheral tissues, including brain, kidney, liver, lung, bone and cardiovascular tissues. SCFA = short chain fatty acids; SLC5A8 = solute carrier family 5 member 8; MCT1 = monocarboxylate transporter 1; GPR41 = G-protein coupled receptor 41; GPR43 = G-protein coupled receptor 43; GPR109A = G-protein coupled receptor 109A; FFAR2 = free fatty acid receptor 2; FFAR3 = free fatty acid receptor 3.

butyrate (Xi et al., 2022). While Caco-2 cells exposed to 5 mM butyrate for 48 h led to increased intestinal permeability and apoptosis proportion (Huang et al., 2014). Therefore, SCFA have both positive and negative effects on intestinal physical barrier by regulating the survival and cellular junctions of intestinal cells.

For the intestinal chemical barrier, it has been reported that propionate and butyrate upregulated the secretion of mucin (MUC) 2 in LS174T cells (Burger-van Paassen et al., 2009). This result was consistent with findings demonstrating that SCFA could stimulate intestinal MUC1 and MUC2 gene expression (Diao et al., 2019). Mucin (MUC2, MUC3 and MUC5AC) gene expression can be induced by butyrate in a variety of patterns (Bai et al., 2010; Gaudier et al., 2004). However, the supplementation of SCFA did not affect the MUC1 and MUC2 mRNA expression in piglets (Zhou et al., 2020). Although the MUC2 gene expression was enhanced in mouse colon exposed to 100 mM butyrate, the mucus thickness was decreased (Gaudier et al., 2009). Hence, the supplementation of SCFA bi-directionally regulates the intestinal chemical barrier mainly via modulating the expression of MUC related genes.

For immunological barrier, a reported review demonstrated that SCFA performed anti-inflammatory effects in the intestine through activating GPR, including GPR41, GPR43, and GPR109A (Venegas et al., 2019). The inflammatory response with inhibiting interleukin (IL)-6 and tumor necrosis factor- α (TNF- α) expression was ameliorated in mice administered butyrate in drinking water and RAW 246.7 cells (Chen et al., 2018). Butyrate also reduced the secretion of pro-inflammatory cytokines in Caco-2 cells, COLO 205 cells, RAW 264.7 cells, and peritoneal macrophages in IL-10-deficient mice (Iraporda et al., 2015; Lee et al., 2017). However, broiler chicks fed formate had a much higher number of spleen lymphocytes (Ragaa et al., 2016). In the mice model, SCFA promoted IL-8 and IL-10 production (Singh et al., 2014; Sun et al., 2018), and the level of IL-22 produced by CD4⁺ cells through GPR41 (Yang et al., 2020b). The gene expression of IL-1 β and IL-17A was elevated in mice administered 80 mM butyrate via enemas (Jimenez et al., 2017). In addition, butyrate inclusion in colostrum caused the immunoglobulin (Ig) G level in calf serum to decrease (Hiltz and Laarman, 2019). Accordingly, SCFA play anti-inflammatory or pro-

inflammatory effects mainly through regulating the expression of cytokines.

For the microbial barrier, weaned pigs fed diets containing 6.4 g/kg formate had a lower abundance of *Lactobacillus*, *Parvimonas*, and *Leuconostoc* (Luise et al., 2017). After calves administering milk replacer with butyrate, the imbalance of intestinal health-related *Mogibacterium* in cecum was restored (O'Hara et al., 2018). The combination of formate and essential oils drastically reduced the counts of *Salmonella* and *Clostridium* in the intestine of broiler chickens (Pathak et al., 2017). The neonatal piglets administrated with butyrate decreased the abundance of *Lactobacillus* in the colon on day 8, although there were only minor alterations in community structure of the intestinal microbiota (Xu et al., 2016). Short chain fatty acids were able to reduce intestinal pH and block the biosynthesis of harmful metabolites by bacteria (Ma et al., 2022). Therefore, SCFA have the ability to inhibit harmful microbiota and maintain intestinal barrier health.

In conclusion, SCFA have positive effects on intestinal health, which are primarily reflected in increasing the expression of TJ proteins including ZO-1, claudins and occludin (physical barrier), promoting the expression of MUC-related genes (chemical barrier), decreasing the expression of pro-inflammatory cytokines (immunological barrier) and inhibiting the growth of harmful microbiota (microbial barrier). Correspondingly, the pathological effects of SCFA are reflected in the increased intestinal permeability, decreased mucus thickness and elevated cytokines (Fig. 3).

Compared with monogastric species (humans, rats, mice, rabbits etc.), ruminant animals (calves, goats, lambs etc.) have an advantage in digesting plant biomass (Hungate, 1966). This advantage comes from the rumen, which occupies for estimated 80% of the total volume of the gastrointestinal tract (Oh et al., 1972). It has been reviewed that exogenous butyrate had beneficial effects on the development of the ruminal epithelium (Niwińska et al., 2017). The ruminal papillae are important for the nutrient absorption in the ruminant epithelium (Gabel et al., 2002). Compared with animals receiving a normal diet, 0.3% sodium butyrate introduction in dry matter led to increased papillary length in calves (Górka et al., 2009, 2011a, 2011b; Kato et al., 2011) and lambs

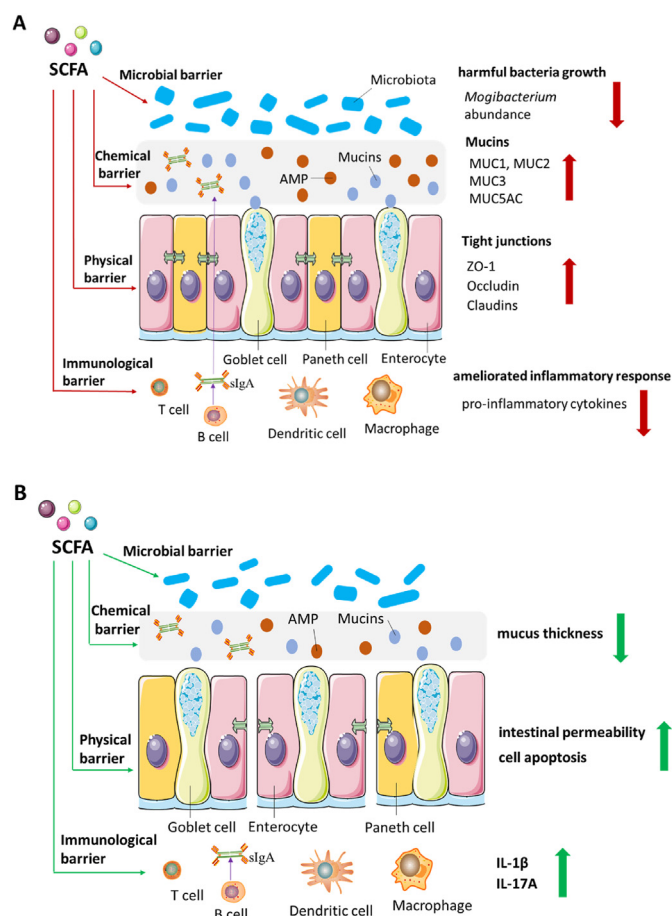


Fig. 3. The double-sided role of SCFA in intestinal health on physical, chemical, immunological, and microbial barrier. (A) The beneficial effects of SCFA on intestinal barrier include increased expression level of tight junction proteins, mucins and decreased harmful bacterial growth as well as the pro-inflammatory cytokines expression. (B) The negative effects of SCFA on intestinal barrier include increased intestinal permeability and pro-inflammatory cytokines as well as the decreased mucus thickness. SCFA = short chain fatty acids; AMP = antimicrobial peptides; MUC = mucin; ZO-1 = zonula occludens-1; slgA = secretory immunoglobulin A; IL-1 β = interleukin-1 β ; IL-17A = interleukin-17A.

(Cavini et al., 2015). Similar results were also shown in goats, where an intraluminal butyrate infusion increased the papillary size, density and surface area (Malhi et al., 2013). The potential mechanisms of butyrate enhancing the papillary development could be explained by inhibiting cell apoptosis (Mentschel et al., 2001), activating the nuclear factors (Naem et al., 2012), and regulating energy delivery (Kuzinski et al., 2012). However, the reports on whether butyrate administration could lead to improvements in calf rearing are still conflicting (Niwińska et al., 2017). Overall, SCFA exerted a double-sided role in both monogastric and ruminant animals.

4. SCFA in gut-organ axes: communication bridge within the body

The controversial effects of SCFA on cancer, obesity and diabetes have been well documented (Cong et al., 2022; Liu et al., 2018). Recently, attention has been drawn to the relationship between SCFA and the health function of the whole body, including the peripheral system (de Vos et al., 2022). Short chain fatty acids are mainly produced by the intestinal microbiota, and the connections between the gut and other organs may be facilitated by gut

microbial metabolites in the form of “axes” (Welch et al., 2022). The concept of “gut-organ axes” is an emerging model that can be used to both diagnose and treat diseases (Ahlawat et al., 2021). Therefore, in the current study, we will summarize the effects of SCFA on human health through the “gut-organ axes” (Fig. 4).

4.1. SCFA in gut-brain axis

Recent studies have shown the effects of SCFA from gut microbiota on the gut-brain axis (Bruning et al., 2020; O’Riordan et al., 2022; Silva et al., 2020). It is clear that SCFA and their metabolites generated in the gut have strong biologically active properties, exerting both beneficial and pathological effects on the brain (Table 2). Short chain fatty acids communicate with the brain directly through their receptors and the vagus nerve. Both the central and peripheral nervous systems have neuronally expressed receptors of SCFA. The presence of SCFA receptor FFAR3 was identified in brain endothelial cells (Hoyle et al., 2018). Activation of FFAR leads to the inhibition of appetite-inducing hypothalamic activity in neuropeptide Y-expressing neurons, which is related to changes in circadian rhythm and appetite (Silva et al., 2020). It also demonstrated that acute oral, rather than intravenous, butyrate could lower the activity of hypothalamic neurons expressing neuropeptide Y, which would inhibit appetite in mice (Li et al., 2018). The results of 500 mg/kg ^{11}C -acetate and PET-CT scanning showed that colonic acetate could be taken up by the brain, and suppressed appetite in C57BL/6 mice (Frost et al., 2014). In addition, intraperitoneal injection of SCFA may also, to variable degrees, diminish appetite. Butyrate is the most effective SCFA, followed by propionate and acetate. This effect was attenuated after the ablation of the vagus nerve, indicating that suvagal afferents were implicated in the inhibition of food intake by SCFA (Goswami et al., 2018). It has been reported that the reduced appetite has been proven to be beneficial for a variety of metabolic diseases, including prevention of obesity, dyslipidemia, and hepatic steatosis development, which promotes host health (Wang et al., 2021).

Short chain fatty acids indirectly signal to the brain through blood brain barrier (BBB) and intestinal immunity. As the main structural barrier between blood and brain, BBB has extremely low cell paracellular permeability and shields the brain from damaging poisons and pathogens to maintain brain homeostasis (O’Riordan et al., 2022). Barrier integrity could be measured by barrier permeability and the level of TJ proteins. In germ-free mice gavaged with butyrate, there was an increase in the production of TJ proteins and a decrease in BBB (Braniste et al., 2014). In addition, the BBB permeability of germ-free mice with SCFA (acetate, propionate, and butyrate) producing bacteria *Clostridium tyrobutyricum* and *Bacteroides thetaiotaomicron* was also reduced (Braniste et al., 2014). Under physiologically normal conditions, brain function is impacted by neuroinflammation, which may be significantly influenced by systemic inflammation. Although immune cell activation and cytokine production have little impact on brain function, systemic infection nevertheless has a considerable impact on the central nervous system, which, in turn, affects cognition and behavior (Cruz-Pereira et al., 2020). It also has been suggested that SCFA may influence immunological cells, which could affect systemic inflammation, peripheral immunity, and ultimately brain function (Dalile et al., 2019). Furthermore, SCFA (acetate, propionate, butyrate, formate, and valerate) individually and collectively lowered the number of cytokines secreted by human THP-1 microglial-like cells, suggesting that SCFA could regulate the function of damaged microglia in Alzheimer’s disease (AD) (Wenzel et al., 2020). However, different SCFA had conflicting effects on inflammation. Butyrate reduced the lipopolysaccharide (LPS)-induced inflammation in rat primary microglia, which was

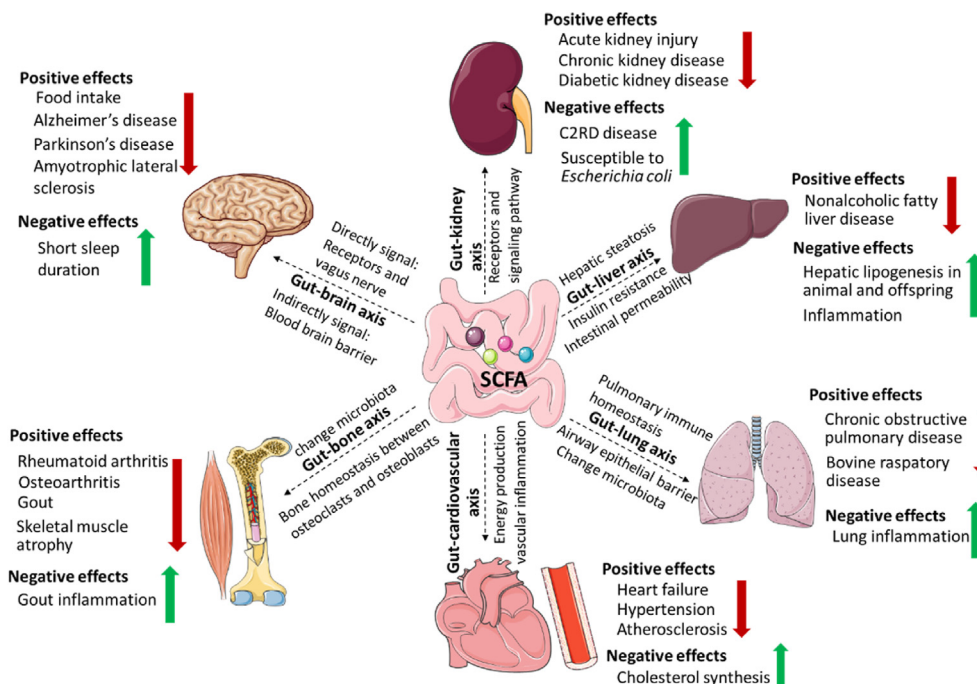


Fig. 4. The double-sided role of SCFA in host health through “gut-organ axes”. The communication between gut and organ linked by SCFA includes “gut-brain axis”, “gut-kidney axis”, “gut-liver axis”, “gut-lung axis”, “gut-bone axis” and “gut-cardiovascular axis”. SCFA = short chain fatty acids.

observed in colon disease, while in murine proliferating N9 microglial cell line, butyrate exerted a pro-inflammatory effect, and these findings were related to the anti-cancer properties of butyrate (Huuskonen et al., 2004).

It is generally known that SCFA have positive effects on neural diseases including AD, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and mood disorders (Mirzaei et al., 2021; Silva et al., 2020). Short chain fatty acids have been identified as the primary signaling molecules in the “brain-gut axis”, a system of bidirectional communication between the central nervous system and the gut (O'Mahony et al., 2015). Studies showed that ischemic stroke decreased intestinal levels of SCFA. In a cerebral ischemia model (9 weeks), transplanting fecal microbiota rich in SCFA into young rats showed a potential therapeutic effect and supplemental butyrate also had a similar effect (Chen et al., 2019). Literature evidence showed that insufficient SCFA produced by the intestinal microbiota in old mice was ameliorated by fecal transplantation of SCFA, which caused a cognitive impairment in comparison to young mice (Lee et al., 2020b). Additionally, the transplantation of four SCFA-producing bacterial strains alleviated brain inflammation in aged mice (18–20 months) with ischemic stroke (Lee et al., 2020a). The youngsters with autism spectrum disorder (ASD) had lower levels of butyrate and more butyrate markers (Liu et al., 2019b). Short chain fatty acids performed the neuroprotective effect in mice by increasing the TJ protein expression and decreasing the level of cytokines (Liu et al., 2021). However, the patients with impaired sleep continuity had greater concentrations of SCFA, including acetate, propionate, and butyrate (Magzal et al., 2021).

Taken together, the positive regulation of the brain by SCFA via the gut-brain axis (receptors, vagus nerve, and BBB) consists of reduced food intake, incidence of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. However, a short sleep duration may be associated with the harmful effects of SCFA on the brain. It has been reported that SCFA in food are absorbed in the stomach and the small intestine to fulfill their nutritional and

physiological roles, but they cannot reach the hindgut under physiological conditions (Braden et al., 1995; Hendry et al., 2010). However, the investigations revealed that oral gavage of SCFA could also play a role in regulating brain function, indicating that the intake of SCFA in food will also have an impact on health. Furthermore, the studies in vivo and in vitro demonstrated that SCFA perform both therapeutic and preventative functions by acting the protective roles via the gut-brain axis whether SCFA are administered before or after modeling.

4.2. SCFA in gut-kidney axis

In this section, the two main forms of renal physiology, acute kidney injury (AKI) and chronic kidney disease (CKD), will be used as examples to highlight the involvement of SCFA in the gut-kidney axis (Table 3). Regarding AKI, butyrate supplementation alleviated renal injury caused by ischemia/reperfusion (I/R) in rats through the upregulated antioxidant and anti-inflammatory activities. Additionally, clinical data revealed that the butyrate level rose coinciding with the recovery of renal function after renal transplantation (Sun et al., 2022). Similarly, acetate and the acetate-producing bacteria also reduced renal I/R injury in C57BL/6 mice (Andrade-Oliveira et al., 2015). By lowering IL-6 level and oxidative stress, two factors involved in the nuclear factor-kappaB (NF-κB) signaling pathway, butyrate was shown to improve kidney function (Machado et al., 2012). In addition, the nephrotoxicity in rats was decreased by butyrate through its antioxidant ability (Sun et al., 2013). Lower levels of butyrate were found in CKD patients compared to healthy controls, which suggests that butyrate supplementation could slow the progression of CKD (Wang et al., 2019). Additionally, propionate partially inhibits renal failure partly through the FFAR2 and FFAR3 signaling pathways (Mikami et al., 2020). It is worth noting that studies in a rat CKD model have shown that high-fiber diets could produce more SCFA and were beneficial for CKD (Kieffer et al., 2016; Vaziri et al., 2014).

Table 2

The studies on two-sided role of SCFA in host health via “gut-brain axis” establishing the connection between gut and brain.

Item	Model/subject	Administration route	Dose and duration	Outcomes	Effects type	Reference
—	30 autistic subjects from China, 20 healthy volunteers as controls	—	—	↓ Fecal acetate and butyrate, as well as butyrate-producing taxa in ASD subjects	Beneficial effect	Liu et al. (2019)
Butyrate, SCFA-produced bacteria	C57BL/6J germ-free adult mice, sterile water as control	Oral gavage	Butyrate (1 g/kg body weight per day) for 3 d, <i>Clostridium tyrobutyricum</i> and <i>Bacteroides thetaiotaomicron</i> for 2 weeks	↓ Blood–brain barrier permeability; ↑ occludin expression in the frontal cortex and hippocampus	Beneficial effect	Braniste et al. (2014)
Acetate	C57BL/6 mice, saline as control	Intraperitoneal injection	500 mg/kg, 1 and 2 h	↓ Acute food intake; ↑ anorectic neuropeptide expression profile	Beneficial effect	Frost et al. (2014)
SCFA	C57BL/6J mice, saline as control	Intraperitoneal injection	Acetate (6 mmol/kg), propionate (6 mmol/kg), butyrate (6 mmol/kg) for 0.5, 1, and 3 h	↓ Food intake	Beneficial effect	Goswami et al. (2018)
SCFA	C57BL/6 mice SAE model, saline as control	Intragastric administration before the model establishment	SCFA (acetate: propionate: butyrate at a ratio of 3:1:1) at 500 mg/kg body weight for 7 d	↓ Behavioral impairment and neuronal degeneration; ↓ IL-1β and IL-6 levels in SAE mice brain	Beneficial effect	Liu et al. (2021)
—	Germ-free C57BL/6 mice	Fecal transplant gavage from aged or young male C57BL/6 mice into germ-free male mice at d 7, 14, 30, and 60	—	↓ Fecal acetate, propionate, and butyrate in aged mice with an aged microbiome	Beneficial effect	Lee et al. (2020a)
Butyrate	Sprague–Dawley rats cerebral ischemia model, saline as control	Intragastrical administration after ischemic modeling	Butyrate (30 mg/kg), 14 d	↓ Volume of the cerebral infarction; ↓ cerebral edema; ↓ intestinal integrity	Beneficial effect	Chen et al. (2019)
Butyrate	E3L.CETP mice received subdiaphragmatic vagotomy surgery, and sham surgery as controls	Intragastric gavage, intravenous injection after a recovery period of 1 week after the surgery	5% (wt/wt), 7 weeks	↓ Food intake; ↓ activity of orexigenic neurons for acute oral administration	Beneficial effect	Li et al. (2018)
SCFA	Human THP-1 cells with LPS (20 ng/mL) plus IFN-γ (100 U/mL)	SCFA were added to THP-1 cells 15 min before their stimulation with LPS plus IFN-γ, and then incubation 48 h	Acetate (5–500 μM), propionate (5–500 μM), butyrate (5–500 μM), formate (5–500 μM), and valerate (5–500 μM) for 48 h	↓ IL-1β, monocyte MCP-1, and TNF-α secretion	Beneficial effect	Wenzel et al. (2020)
—	Aged stroke mice	FTG from aged or young male C57BL/6 mice into aged stroke mice for 3 d	—	↑ SCFA-producers in young mice; ↓ poststroke neurological deficits, inflammation in aged stroke mice; ↑ gut, brain and plasma SCFA concentrations in aged stroke mice	Beneficial effect	Lee et al. (2020b)
Butyrate	N9 microglial cells, rat primary microglia	N9 cells incubated with LPS and butyrate simultaneously for 22 h, butyrate-pretreated (for 22 h) in rat primary microglia cultures and then incubated with 5 μg/mL LPS	Butyrate (0.6 mM) for N9 cells, butyrate (2.5 mM) for rat primary microglia	↑ LPS-induced IL-6 level in N9 cells; ↓ IL-6 level in rat primary microglia	Beneficial effect	Huuskonen et al. (2004)
—	Fifty-nine participants with insomnia symptoms (≥ 65 years)	Participants were divided into short and normal sleep duration phenotypes for a 2-week period	—	↑ Short sleep duration in insomnia is associated with an increase in SCFA	Pathological effect	Magzal et al. (2021)

ASD = autism spectrum disorder; SCFA = short chain fatty acids; SAE = sepsis-associated encephalopathy; IL-1β = interleukin-1β; IL-6 = interleukin-6; LPS = lipopolysaccharide; IFN-γ = interferon-γ; MCP-1 = monocyte chemoattractant protein-1; TNF-α = tumor necrosis factor-α; FTG = fecal transplant gavage. ↑ represents increase. ↓ represents decrease.

Short chain fatty acids have also been regarded as potential pharmacological candidates for attenuating CKD progression ([Felizardo et al., 2019](#)).

Apart from AKI and CKD, diabetic kidney disease (DKD) has gradually grown in popularity as a research topic. A lower SCFA level in the serum and feces of DKD patients was reported ([Zhong](#)

Table 3

The studies on two-sided role of SCFA in host health via “gut-kidney axis” establishing the connection between gut and kidney.

Item	Model/subject	Administration route	Dose and duration	Outcomes	Effects type	Reference
Butyrate	Sprague–Dawley rats AKI model induced by renal I/R, saline as control	Tail vein injection 30 min prior to the renal I/R operation	100 mg/kg, 6, 12, and 24 h	↑ Function and structure of kidney	Beneficial effect	Sun et al. (2022)
—	Thirty-two patients who underwent allograft renal transplantation	—	—	↑ Fecal butyrate; ↑ renal function after renal transplant recovery	Beneficial effect	Sun et al. (2022)
Acetate, <i>Bifidobacterium longum</i> or <i>Bifidobacterium adolescentis</i>	C57BL/6 mice AKI model induced by I/R	Bacteria gavage for 10 d before kidney IRI	Bacteria gavage	↓ Acute kidney injury induced by IR	Beneficial effect	Andrade-Oliveira et al. (2015)
SCFA	C57BL/6 mice AKI model induced by I/R, saline as control	0.5 h before I/R operation	Acetate (200 mg/kg), propionate (200 mg/kg), and butyrate (200 mg/kg)	↓ Serum level of creatinine and urea; ↑ kidney function after IRI, and acetate performed the best protection.	Beneficial effect	Andrade-Oliveira et al. (2015)
Butyrate	Wistar rats AKI model induced by metaglumina diatrizoate sodium, saline as control	Tail vein injection 6 h before modeling	500 mg/kg, 6 d	↓ Serum creatinine level and IL-6 level	Beneficial effect	Machado et al. (2012)
Butyrate	Sprague–Dawley rats nephrotoxicity model induced by gentamicin	Intraperitoneal injection 30 min prior to gentamicin injection	50, 100, 200 mg/kg, 8 d	↑ Activities of superoxide dismutase, catalase; ↓ glutathione and nephrotoxicity	Beneficial effect	Sun et al. (2013)
—	One hundred and twenty-seven patients with CKD and 63 healthy 33 controls	—	—	↓ Serum SCFA levels in CKD patients, and an inverse correlation between butyrate level and renal function	Beneficial effect	Wang et al. (2019)
Butyrate	Sprague–Dawley rats, the 5/6 nephrectomized model	0.5% butyrate administered by gavage after one week surgery recovery	313 μL/kg, 8 weeks	↓ Renal fibrosis and delayed CKD progression	Beneficial effect	Wang et al. (2019)
Propionate	C57BL/6 mice, <i>FFA2^{-/-}</i> mice, and <i>FFA3^{-/-}</i> mice CKD model induced by adenine	0.5% or 1.0% propionate via drinking water for 6 weeks accompanying model construction	0.5% or 1.0%, 6 weeks	↓ Kidney damage; ↓ serum level of creatinine and blood urea nitrogen	Beneficial effect	Mikami et al. (2020)
Diets	Sprague–Dawley rats CKD model induced by adenine	Amylopectin (low-fiber control) and high fermentable fiber for 3 weeks	—	↑ Kidney function; ↑ gut permeability indexes	Beneficial effect	Kieffer et al. (2016)
Diets	Sprague–Dawley rats CKD model induced by adenine	Amylopectin (low-fiber control) and high fermentable fiber for 3 weeks	—	↓ CKD progression; ↓ oxidative stress and inflammation	Beneficial effect	Vaziri et al. (2014)
—	Thirty participants with DKD, 30 normal controls	—	—	↓ Fecal acetate, propionate, butyrate and total SCFA levels in DKD group	Beneficial effect	Zhong et al. (2021)
Diets, SCFA	C57BL/6 mice, <i>GPR43^{-/-}</i> mice, and <i>GPR109A^{-/-}</i> mice diabetes model induced by streptozotocin	High-fiber, normal chow, zero-fiber diets, SCFA in drinking water after modeling	Acetate (100 mM), butyrate (50 mM), and propionate (100 mM) for 3 weeks	↓ Diabetic nephropathy; ↑ SCFA-producing bacteria; ↑ SCFA production	Beneficial effect	Li et al. (2020)
SCFA	Sprague Dawley rats renal stone model induced by ethylene glycol	Acetate, propionate, and butyrate in drinking water	4 weeks	↓ Renal crystals	Beneficial effect	Liu et al. (2020)
—	Five occasional stones patients, 5 recurrent stones patients, 5 non-kidney stone control	—	—	↓ SCFA-producing gut bacteria; ↓ metabolic pathways associated with SCFA production in kidney stone patients	Beneficial effect	Liu et al. (2020)
SCFA	C57BL/6 mice, <i>GPR43^{-/-}</i> mice, and <i>GPR41^{-/-}</i> mice	Acetate, propionate, and butyrate in drinking water	Acetate (100, 150, and 200 mM), propionate (200 mM), and butyrate (200 mM) for 6 weeks	↑ Renal hydronephrosis disease; ↑ hydronephrosis and hyperplasia in kidney and ureter tissues	Pathological effect	Park et al. (2016)

AKI = acute kidney injury; I/R = ischemia/reperfusion; SCFA = short chain fatty acids; IL-6 = interleukin-6; CKD = chronic kidney disease; DKD = diabetic kidney disease. ↑ represents increase. ↓ represents decrease.

Table 4

The studies on two-sided role of SCFA in host health via “gut-liver axis” establishing the connection between gut and liver.

Item	Model/subject	Administration route	Dose and duration	Outcomes	Effects type	Reference
Butyrate	C57BL/6J mice NAFLD model	Gavage	Sodium butyrate (0.12 g/mL), 6 weeks	↓ NASH development, which may be driven by the protective gut microbiome and metabolome	Beneficial effect	Ye et al. (2018)
SCFA	Male C57BL/6J mice, PPAR lox/ lox mice, 2 months of age	Dietary intake	Acetate, propionate or butyrate was incorporated into diet at 5% (wt/wt)	↓ PPAR γ expression in the liver; ↓ hepatic triglyceride concentrations	Beneficial effect	den Besten et al. (2015)
Butyrate	C57BL/6J mice NAFLD model, liquid as control	Oral consumption	Sodium butyrate (0.6 g/ kg body weight per day), 6 weeks	↓ Inflammation in the liver; ↓ development of NASH	Beneficial effect	Jin et al. (2015)
Acetate	Male wistar rats, water as control	Oral gavage	Sodium acetate (200 mg/kg), 8 weeks	↓ Xanthine oxidase activity, and performs hepatoprotection	Beneficial effect	Dangana et al. (2020)
Acetate	Hyla rabbits, saline as control	Subcutaneous injection	Acetate (2 g/kg body weight per day, one injection each day), 4 d	↓ Intramuscular triglyceride level; ↑ fatty acid uptake; ↑ fatty acid oxidation	Beneficial effect	Liu and Fu (2019)
SCFA	Thirteen overweight and obese, 20–50 years old Caucasian men	Rectal infusion	SCFA mixtures (acetate, propionate and butyrate), 4 clinical investigation days	↑ Fat oxidation, energy expenditure and PYY; ↓ lipolysis in overweight/ obese men	Beneficial effect	Araujo et al. (2020)
Propionate	Human HepG2 hepatocytes	Following propionate treatment of the cells for 24 h	Propionate (0, 0.25, 0.5 mM) for HepG2 cells	↓ Gene expression of gluconeogenic enzymes independent of insulin signaling	Beneficial effect	Yoshida et al. (2019)
Propionate, butyrate	Duroc × Landrace × Yorkshire pigs (50% male) weaned at day 28	Dietary intake	Basal diet plus 1 g propionate/kg, or plus 1 g butyrate/kg diet for 14 d	↑ Serum PYY concentration; ↑ lipid metabolism	Beneficial effect	
SCFA	Multi-organ model of UC ex vivo	—	20 mM of SCFA	↑ Effector function of activated CD4 ⁺ T cells; ↓ acute CD4 ⁺ T cell- dependent UC inflammation; ↑ risk of liver injury	Pathological effect	Trapezar et al. (2020)
Butyrate	Primiparous purebred female SD rats	Dietary intake	1% sodium butyrate diet	↑ Promotes maternal fat mobilization, ↑ fatty acid uptake and lipid accumulation in the liver of offspring	Pathological effect	Zhou et al. (2016)

NAFLD = nonalcoholic fatty liver disease; NASH = non-alcoholic hepatitis; SCFA = short chain fatty acids; PPAR = peroxisome proliferator-activated receptor; PYY = peptide YY; UC = ulcerative colitis. ↑ represents increase. ↓ represents decrease.

et al., 2021). Through FFAR2 and GPR109A signaling pathways, a high-fiber diet and SCFA (acetate, butyrate, and propionate) protected diabetic mice from developing diabetic nephropathy. Short chain fatty acids also reduced the expression of pro-inflammatory cytokines in vitro, demonstrating SCFA's ability to prevent diabetic nephropathy (Li et al., 2020). The renal crystals of rats with renal calcium oxalate stones were reduced after administering with SCFA, and kidney stone patients had lower abundance of SCFA-producing bacteria and the metabolic pathway linked to SCFA production (Liu et al., 2020). A review has proved that SCFA treatment could be a new therapeutic approach for kidney injury induced by a gut-derived inflammatory response (Huang et al., 2017).

However, the literature continues to suggest that SCFA have a certain detrimental impact on kidney function (Table 3). Acetate- or C2-induced renal disease, also known as C2RD disease, is a T cell-mediated renal disease with progressive ureteritis and hydronephrosis. It is caused by the chronic administration of SCFA at levels higher than the physiological level (Park et al., 2016). Additionally, mice fed a high dietary fiber diet had a higher blood level of butyrate and fewer *Escherichia* species, which made them more susceptible to *Escherichia coli* and increased Gb3 protein level in the

kidney, eventually leading to severe kidney damage (Zumbrun et al., 2014, 2013).

In conclusion, SCFA regulate kidney function by altering receptors and associated signaling pathways in the gut-kidney axis. Short chain fatty acids have a dual effect on kidney function, reducing the severity of AKI, CKD, and DKD (positive regulation) as well as increasing inflammation and bacterial susceptibility in renal hydronephrosis (C2RD disease) (negative regulation). The tail vein injection of SCFA plays a protective effect on renal diseases, which is consistent with the findings that high fiber diets may be beneficial for the kidney via the gut-kidney axis, which could produce more SCFA in the circulatory system. In addition, based on the mode of administration, SCFA have a larger preventive effect on the liver than a therapeutic effect.

4.3. SCFA in gut-liver axis

Nonalcoholic fatty liver disease (NAFLD), including simple steatosis, non-alcoholic hepatitis (NASH) and liver cirrhosis, has become the most common liver disease in the world (Farrell and Larter, 2006; Loomba and Sanyal, 2013). It has become an important cause of chronic liver disease in developed countries, such as

Europe and the United States and rich regions of China, which can seriously increase the occurrence of hepatocellular cancer (Behary et al., 2021; Wong et al., 2014). The link between gut bacteria dysbiosis and NASH and NAFLD has been documented (Leung et al., 2016; Wigg et al., 2001). The primary sclerosing cholangitis may potentially be linked to ulcerative colitis via the gut-liver axis (Loftus et al., 2005). Butyrate reverses the development of NASH, which is partly associated with the changes gut microbiome (Ye et al., 2018). Based on the reported studies, we propose that SCFA might contribute to preventing the progression of NAFLD via different mechanisms through the gut-liver axis (Table 4).

The first is that SCFA affect hepatic steatosis. In mice, feeding a diet containing 5% SCFA (acetate, propionate or butyrate) tripled lipid oxidation, highly elevating the oxidative state leading to decreased liver lipid synthesis in a peroxisome proliferator-activated receptor γ (PPAR γ)-dependent manner (den Besten et al., 2015). Gastric administration of butyrate in mice reduced lipid deposition in the liver, markedly reducing inflammation (Jin et al., 2015). Likewise, the supplementation of acetate protected rats from nicotine-induced excess liver lipid by inhibiting xanthine oxidase activity (Dangana et al., 2020). In the liver of rabbits, acetate boosted lipolysis and fatty acid oxidation, preventing lipid accumulation (Liu et al., 2019a). Acetate produced by gut microbiota could inhibit chylomicron secretion, resulting in reduced lipid flow into the circulatory system and alleviated the severity of NAFLD (Araujo et al., 2020). There is evidence that intestinal microbiota and NAFLD is interconnected. Thus, it was found that a reduced abundance of Bacteroidetes (producer of SCFA) was shown in NAFLD adults, compared with healthy controls (Mouzaki et al., 2013). Therefore, both SCFA and high-fiber diets could encourage the proliferation of Bacteroidetes bacteria, relieving liver disease (de Wit et al., 2012; Turnbaugh et al., 2006).

Secondly, another important piece of evidence relates to the ability of SCFA to reduce insulin resistance. Since the liver is the organ responsible for storing and metabolizing glucose, insulin resistance results from the liver's inefficient use of glucose (Zhang et al., 2022a). Short chain fatty acids in the liver could modulate hepatic insulin sensitivity via the AMPK signaling pathway. Additionally, SCFA could bind to GPR41 and GPR43 receptors in hepatocytes thereby suppressing AMPK-dependent gluconeogenesis (den Besten et al., 2015; Tan et al., 2021). Propionate inhibits gluconeogenesis via binding with hepatic GPR43 and activates the AMPK signaling pathway (Yoshida et al., 2019).

Thirdly, SCFA reverse intestinal permeability. According to in vivo findings, a high-fat diet induced hepatic steatosis, which was linked to higher intestinal permeability (Cani et al., 2007). Additionally, the high-fat diet model also revealed a relationship between NAFLD and intestinal permeability; specifically, the severity of steatohepatitis increased when colitis was induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS), as shown by the liver enzyme levels and the NAFLD Activity Score (NAS) (Mao et al., 2015). Given that SCFA can reverse intestinal permeability, it is possible to hypothesize that SCFA can prevent NAFLD by protecting the intestinal barrier.

However, the impact of SCFA on the liver also has two sides. It has been reported that microbiota-derived excessive acetate may encourage liver lipogenesis (Table 4). The excess SCFA produced by the gut microbiota is an extra energy source contributing to liver fat accumulation (Murugesan et al., 2018). Besides acetate, another study showed that higher propionate synthesis boosted hepatic lipogenesis (Gao et al., 2019). Using a multi-organ ex vivo model, it was discovered that SCFA could lead to intestinal barrier breakdown and liver injury in the process of acute T cell-mediated inflammation (Trapecar et al., 2020). Additionally, maternal butyrate supplementation during pregnancy and lactation may cause lipid accumulation in the liver of the offspring (Zhou et al., 2016).

Therefore, SCFA modulate hepatic steatosis, insulin resistance, and intestinal permeability through the gut-liver axis to regulate liver function. The negative effects include increased hepatic lipogenesis and inflammation, whereas favorable effects include halting the progression of NAFLD. Different from the brain and kidney, adding SCFA to the diet while simulating liver disease may have protective effects.

4.4. SCFA in the gut-lung axis

Although the signal of the gut-lung axis has a bi-directional response, the majority of the communication between the two organs occurs from the gut to the lung (Dang and Marsland, 2019). It has been reported that the impairment of lung function may be associated with the deterioration of the diversification of the intestinal microbiota (Chiu et al., 2022). Additionally, the presence of SCFA in the sputum further supported the relationship between the gut and the lung (Ghorbani et al., 2015). The two-sided effects of SCFA in the gut-lung axis are summarized in Table 5.

It has been reported that 500 mM butyrate had an anti-inflammatory effect in the lung and prevented excessive airway infiltration by reducing lung macrophage- and monocyte-produced C-X-C motif chemokine ligand 1 (CXCL1) expression in female mice (Trompette et al., 2018). Besides the lung immune defense effects, SCFA (acetate, propionate, and butyrate) also protect the lung via maintaining the airway epithelial barrier by increasing the TJ protein expression in human bronchial epithelial 16HBE cells (Richards et al., 2021). Chronic obstructive pulmonary disease (COPD) is one of the most widespread respiratory diseases. The role of SCFA in the prevention and treatment of COPD cannot be overlooked (Kotlyarov, 2022). Emphysema is a typical feature of COPD, and experimental animal models have shown a connection between nutritional deficiency and alveolar tissue destruction leading to emphysema (Wright et al., 2008). A high-fiber diet attenuated emphysema-associated pathological changes in mice with cigarette-exposed emphysema, which could partly be explained by increased production of SCFA, including acetate, propionate, and butyrate (Jang et al., 2021). In addition, in a rat hypoxia model, butyrate treatment reduced the accumulation of CD68⁺ in the lung alveoli as well as CD68⁺ and CD163⁺ pulmonary macrophages in lung interstitial microvascular cells (Karooor et al., 2021). Emphysema has been linked to interalveolar septal vascularization, which could be brought on by apoptosis of alveolar epithelial and endothelial cells (Petrache and Petrusca, 2013). Short chain fatty acids may therefore prevent emphysema by protecting endothelial cells and maintaining pulmonary immune homeostasis (Kotlyarov, 2022).

Exacerbations are the other characteristic of COPD. The structural disturbance of the bronchial microbiota is connected to the worsening of COPD (Kotlyarov and Kotlyarova, 2021). The microorganism's colonization in the bronchi is necessary to maintain the immunological tension of the lung. The available data indicate that there are some links between the gut and lung microbiota (Madan et al., 2012). Studies have revealed that diet could alter the microflora in the intestine as well as the microflora in the respiratory tract (Madan et al., 2012; Trompette et al., 2014). Short chain fatty acids have been confirmed to directly affect microorganisms and change their virulence (Machado et al., 2021). High quantities of SCFA dramatically slowed down *Pseudomonas aeruginosa* development (Ghorbani et al., 2015).

It is worth noting that SCFA have both anti-inflammation and pro-inflammatory functions. Results from both in vivo and in vitro experiments have confirmed that SCFA (acetate, propionate, and butyrate) could inhibit Th2 responses by directly modulating T and dendritic cells, thus ameliorating the gut dysbiosis-driven lung

Table 5

The studies on two-sided role of SCFA in host health via “gut-lung axis” establishing the connection between gut and lung.

Item	Model/subject	Administration route	Dose and duration	Outcomes	Effects type	Reference
SCFA	Sputum samples from cystic fibrosis patients, A549, CFBE, corrCFBE or primary human bronchial epithelial cells	Cells incubated for 1 h with various SCFA prior to cytomix stimulation	SCFA: colonic lumen (10–50 mM) cystic fibrosis airways (0.1–5 mM)	↓ Airway epithelium inflammatory responses, ↑ iNOS and <i>Pseudomonas aeruginosa</i> growth	Beneficial effect	Ghorbani et al. (2015)
Butyrate	Adult female mice fed a low-fiber diet for 4 weeks then received butyrate	Oral gavage	Sodium butyrate (500 mM) for 2 weeks	Balancing innate and adaptive immunity; ↓ influenza infection; ↓ immune-associated pathology	Beneficial effect	Trompette et al. (2018)
SCFA	Differentiating human bronchial epithelial cells (16HBE)	16HBE cells were stimulated with IL-4, IL-13 or house dust mite, then with SCFA	10 mM acetate, 0.5 mM propionate or 1 mM butyrate	↑ Lung immune defense effects; ↑ tight junction proteins expression in the airway epithelial barrier	Beneficial effect	Richards et al. (2021)
SCFA	Female C57BL/6 mice cigarette smoking-exposed emphysema model	Mice with standard AIN 76A diet, high-cellulose and high-pectin diet	—	↓ Emphysema development; ↓ local and systemic inflammation	Beneficial effect	Jang et al. (2021)
Butyrate	Sprague–Dawley rat model of hypoxic pH, rat microvascular endothelial cells	SD rat: oral gavage; cells: cells were pretreated with butyrate for either 2 or 24 h, followed by either LPS or TNF- α stimulation	SD rat: butyrate (220 and 2200 mg/kg intake); cells: butyrate (1 mM)	↓ Accumulation of CD68 ⁺ in the lung alveoli; ↓ CD68 ⁺ and CD163 ⁺ pulmonary macrophages in lung interstitial	Beneficial effect	Karoo et al. (2021)
SCFA	C57BL/6 female mice treated with different fiber content diet	Oral gavage in drinking water before exposed to house dust mite extract	Sodium acetate or sodium propionate (200 mM) for 3 weeks	Shape the immunological environment in the lung; ↓ severity of allergic inflammation	Beneficial effect	Trompette et al. (2014)
SCFA	Vancomycin-treated mice, autoclaved water as control	Oral gavage	40 mM butyrate, 67.5 mM acetate plus 25.9 mM propionate	↓ Th2 responses to modulate the systemic immune response	Beneficial effect	Cait et al. (2018)
SCFA	Primary HLF and ASM cells with TNF- α (1 ng/mL)	Cells stimulated with SCFA for 24 or 96 h, with or without TNF- α for another 12 or 24 h	Acetate (0.5–25 mM), propionate (0.5–25 mM), butyrate (0.01–10 mM)	↑ TNF- α -induced inflammatory responses; ↑ IL-6 and C-X-C motif chemokine ligand 8 release via activation of FFAR3 and p38 MAPK signaling	Pathological effect	Rufting et al. (2019)
SCFA	Peripheral blood mononuclear cells or neutrophils	Cells stimulated with LPS alone or in combination with various SCFA	SCFA (0–20 mM) for 18 h	↑ Pro-inflammatory milieu in the lower genital tract	Pathological effect	Mirmonsef et al. (2012)

SCFA = short chain fatty acids; iNOS = inducible nitric oxide synthase; IL-4 = interleukin-4; IL-13 = interleukin-13; LPS = lipopolysaccharide; TNF- α = tumor necrosis factor- α ; HLF = human lung fibroblasts; IL-6 = interleukin-6; ASM = airway smooth muscle; FFAR3 = free fatty acid receptor 3; MAPK = mitogen-activated protein kinase kinases; LPS = lipopolysaccharides. ↑ represents increase. ↓ represents decrease.

inflammation (Cait et al., 2018). However, the pro-inflammatory effects of SCFA (acetate, propionate, and butyrate) were shown in human primary lung fibroblast cells and airway smooth muscle cells via the p38 MAPK signaling pathway (Rufting et al., 2019). The high concentrations of SCFA in cells increased the secretion of pro-inflammatory cytokines (Mirmonsef et al., 2012).

Therefore, a reduction in the severity and incidence of COPD is a favorable effect of SCFA on lung function, whereas the rise in lung inflammation is a negative effect. These effects are mainly achieved by the ability of SCFA to regulate pulmonary immune homeostasis, airway epithelial barrier and intestinal microbiota.

4.5. SCFA in gut-bone axis

For the body to operate properly overall, bones are essential. Bones are not only essential in supporting the body frame, but also for protecting important organs, acting as a mineral pool of calcium homeostasis, and providing a setting for the development of bone marrow, cytokines and growth factors (Medina-Gomez, 2018). Bone health is significantly impacted by intestinal microbiota and

its metabolites. Recent studies have revealed a complex relationship between the gut and bone health (Ahlawat et al., 2021). The effects of SCFA on the gut-bone axis are shown in Table 6.

The results of intestinal microbiota and microCT analysis showed that the positive effect of raw potato starch on bone mass might be related to the higher proportion of Firmicutes and the production of SCFA in the cecum, which led to the reduction of the expression of the pro-inflammatory genes in the intestine and bone marrow, thereby inhibiting cytokine-mediated osteoclast bone resorption in Cherry Valley male ducks (Zhang et al., 2022a). Studies have shown a connection between bone mineral density and gut microbiota, showing that Crohn's disease and obesity increase the risk of fractures (Villa et al., 2017). Hence it may be postulated that SCFA could protect bone via maintaining bone homeostasis and skeletal muscle function.

The two main components of bone homeostasis, osteoclasts and osteoblasts, act on bone resorption and formation, respectively. Reduced bone density and an imbalance in bone homeostasis are characterized by chronic inflammatory disorders like rheumatoid arthritis, which is due to increased bone resorption brought on by

Table 6

The studies on two-sided role of SCFA in host health via “gut-bone axis” establishing the connection between gut and bone.

Item	Model/subject	Administration route	Dose and duration	Outcomes	Effects type	Reference
SCFA	1-d-old Cherry Valley male ducks, saline as control	0% RPS diets, SCFA in drinking water	SCFA (67.5 mM acetate, 38.8 mM propionate, 22.8 mM butyrate) for 14 d	↓ Pro-inflammatory genes expression in both gut and bone marrow; ↓ osteoclastic bone resorption	Beneficial effect	Zhang et al. (2022)
SCFA	C57BL/6J female mice, ovariectomized mice, arthritis model	Drinking water	150 mM acetate, propionate and butyrate for 8 weeks	↑ Bone mass; ↓ postmenopausal and inflammation-induced bone loss; ↓ osteoclast differentiation and bone resorption	Beneficial effect	Lucas et al. (2018)
Butyrate	Rat bone marrow cells and RAW-D cell	RAW-D cells were preincubated with butyrate, then stimulated with TNF- α for 30 min	butyrate (1 mM) for 24 h	↓ Osteoclast-specific signals; ↓ HDAC activity regulates the process of osteoclastogenesis	Beneficial effect	Rahman et al. (2003)
Acetate	Male C57BL/6 and C57BL/6 GFP Het mice gout model induced by MSU	Mice were treated with acetate, butyrate, and propionate during the 5 d before MSU challenged	150 mM acetate in drinking water, butyrate (50 mM) or propionate (25 mM) by oral gavage	↑ Caspase-dependent neutrophil apoptosis, efferocytosis, and ↓ inflammation	Beneficial effect	Vieira et al. (2017)
Butyrate	Dietary-obese C57BL/6J mice	Diet supplementation at 5% (wt/wt) in the high-fat diet	Sodium butyrate at 5 g/kg per day at the normal daily rate of calorie intake	↓ Diet-induced insulin resistance in mouse; ↑ energy expenditure; ↑ mitochondria function	Beneficial effect	Gao et al. (2009)
Butyrate	Five-week-old male C57BL/6J mice	low-fat diet (LFD), high-fat diet (HFD) or HFD supplemented with butyrate	5% butyrate (wt/wt) for 10 weeks	↑ Insulin-sensitizing and anti-obesogenic; ↑ muscle mitochondrial function	Beneficial effect	Henagan et al. (2015)
Acetate	Six-week-old C57BL/6 mice	Drinking water	100, 200 or 300 mM sodium for 3 weeks	↓ Colitis severity	Beneficial effect	Macia et al. (2015)
Butyrate	Four-week-old male db/db and db/m mice	—	1 g/kg per day at the normal daily rate of calorie intake for 12 weeks	↓ Muscle atrophy induced by diabetic nephropathy by activating the FFA2 receptor-mediated PI3K/Akt/mTOR pathway	Beneficial effect	Tang et al. (2022)

SCFA = short chain fatty acids; TNF- α = tumor necrosis factor- α ; RPS = raw potato starch; HDAC = histone deacetylases; MSU = monosodium urate; FFA = free fatty acid; PI3K/Akt/mTOR = phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin. ↑ represents increase. ↓ represents decrease.

the activation of osteoclasts. A reported study showed that SCFA, especially propionate and butyrate, prevented the development of osteoclast precursor cells in bone marrow by inhibiting the receptor activator of nuclear factor- κ B ligand (RANKL) signaling, without affecting osteoblasts (Lucas et al., 2018). In addition, it has been demonstrated that butyrate inhibited histone deacetylase (HDAC) and its downstream genes, hence suppressing the formation of osteoclasts in rat bone marrow cells and RAW-D cells (Rahman et al., 2003).

Systemic autoimmune diseases, including rheumatoid arthritis, osteoarthritis and gout are characterized by the progressive damage of bone and cartilage as well as chronic joint inflammation. Recent studies have demonstrated that gut microbiota and their metabolites are linked to these autoimmune diseases (Abdollahi-Roodsaz et al., 2016; Chang et al., 2001; Kau et al., 2011). The increased fiber intake has been confirmed to have positive effects on alleviating gout development, which could be explained by the production of SCFA (Lyu et al., 2003). Additionally, a study showed that a high-fiber diet and acetate consumption reduced gout-related inflammation induced by monosodium urate crystals. This relationship is related to the acetate's capacity to trigger neutrophil apoptosis (Vieira et al., 2017). The preventive benefits of high fiber diets and SCFA also shown in the experimental mice with arthritis (Lucas et al., 2018).

Regarding the advantageous effects of butyrate administration on skeletal muscle, the study discovered that C57BL/6J mice supplemented with butyrate showed increased gene expression necessary for beneficial mitochondrial adaptation, including peroxisome proliferator-activated receptor- γ coactivator (PGC)-1 α , peroxisome proliferators-activated receptors δ (PPAR δ), and carnitine palmitoyltransferase (CPT)1b, and also prevented the

incomplete oxidation of skeletal muscle caused by high-fat diets (Gao et al., 2009; Henagan et al., 2015). Additionally, butyrate decreased the skeletal muscle atrophy induced by diabetic nephropathy through phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway in mice (Tang et al., 2022). Therefore, by enhancing the skeletal muscle oxidation capacity, butyrate could partially prevent obesity and insulin resistance.

Again SCFA appear to have both beneficial and pathological impacts on bone homeostasis. The results on germ-free mice indicated that insufficient SCFA levels or GPR43 receptor deficiency could lead to defects in inflammasome assembly, which impaired gout inflammation of the knee (Vieira et al., 2015). Similarly, a study demonstrated that the lack of microbiota and SCFA damaged the inflammasome assembly in epithelial cells, impairing their capacity to defend against harmful stimuli (Macia et al., 2015).

In summary, SCFA in the gut-bone axis regulate bone function by modulating intestinal microbiota and bone homeostasis between osteoclasts and osteoblasts. Short chain fatty acids have a dual effect on bone function that includes both a reduction in the severity of rheumatoid arthritis, osteoarthritis, gout, and skeletal muscle atrophy (positive regulation) as well as an increase in gout inflammation (negative regulation). Apart from butyrate, the most studies SCFA, in vivo studies have proved that acetate is beneficial for host bone health with preventive and therapeutic effects.

4.6. SCFA in the gut-cardiovascular axis

There are many risk factors for cardiovascular diseases, including diet. Studies have revealed that intestinal microbiota are an extragenomic contributor to cardiovascular diseases (Tuohy

Table 7

The studies on two-sided role of SCFA in host health via “gut-cardiovascular axis” establishing the connection between gut and cardiovascular.

Item	Model/subject	Administration route	Dose and duration	Outcomes	Effects type	Reference
Free fatty acid	110 patients with or without heart failure	Metabolomics on blood from artery, coronary sinus, and femoral vein	—	Uptake of acetate was directly proportional to circulating concentrations in both heart	Beneficial effect	Murashige et al. (2020)
Butyrate	Cardiac hypertrophy Sprague–Dawley rats, sham operated as control	Hearts perfused	A mix of 0.5 mM butyrate and 0.5 mM 3-hydroxybutyrate	↑ Oxidization in failing hearts	Beneficial effect	Carley et al. (2021)
Acetate	Long Evans rats model of OSA, sham rats receiving PBS as control	Chronic infused acetate into the cecum	20 μmol/(kg·min) and 2 weeks	↑ Cecal acetate concentrations; ↓ OSA on the microbiota, gut, brain, and blood pressure	Beneficial effect	Ganesh et al. (2018)
Acetate	Male C57BL/6 mice hypertensive model	Drinking water	200 mM magnesium acetate and 3 weeks	Change the gut microbiota; ↓ development of hypertension and heart failure mice	Beneficial effect	Marques et al. (2017)
Propionate	Wild-type and <i>Apoe</i> ^{−/−} mice	Drinking water	200 mM	↓ Cardiac hypertrophy, fibrosis, vascular dysfunction, and hypertension	Beneficial effect	Bartolomaeus et al. (2019)
①SCFA ②Sodium acetate	①Male and female C57BL/6J mice ②Male C57BL/6J male mice	①Intraperitoneal injection ②Heart perfused	①1 g/kg ②1 M	① ↓ Mean arterial pressure, HR, and cardiac contractility. ② Acetate ↓ HR after extended exposure	Beneficial effect	Poll et al. (2021)
SCFA	C57BL/6 GPR41 WT male mice and GPR41 KO mice	—	—	↓ Hypotensive response	Beneficial effect	Natarajan et al. (2016)
Butyrate	14–16 weeks old wistar rats	Administration into the colon	1.4 (<i>n</i> = 5), 2.8 (<i>n</i> = 5) and 5.6 mmol/kg (<i>n</i> = 5)	↑ Hypotensive effect, which seems to be mediated by the colon afferent nervous signaling and GPR41/43 receptors	Beneficial effect	Onyszkiewicz et al. (2019)
Propionate	①16 weeks female C57BL/6, <i>Apoe</i> ^{−/−} mice ②62 individuals with baseline LDL cholesterol levels >115 mg/dL	①Oral gavage ②Oral	①150 mM calcium propionate and four weeks ②Propionate (500 mg) twice daily for 8 weeks	① ↓ High-fat diet-induced hypercholesterolaemia and atherosclerosis in <i>Apoe</i> ^{−/−} mice ② ↓ Serum LDL and total cholesterol in hypercholesterolaemic humans	Beneficial effect	Haghikia et al. (2022)
Butyrate	Twenty 6-week-old male apoprotein E deficient (<i>Apoe</i> ^{−/−}) mice	Diet	1% butyrate-supplemented diet (butyrate) for 10 weeks	↓ Inflammation and activation of NF-κB and atherosclerosis	Beneficial effect	Aguilar et al. (2014)

SCFA = short chain fatty acids; OSA = obstructive sleep apnea; PBS = phosphate buffer saline; HR = heart rate; GPR = G-protein-coupled receptor; WT = wild type; KO = knock out; LDL = low-density lipoprotein; NF-κB = nuclear factor-kappaB. ↑ represents increase. ↓ represents decrease.

et al., 2014). The majority of risk factors for cardiovascular diseases have the potential to result in microecological disorders linked to intestinal inflammation and the reduction of intestinal barrier integrity, which would increase the number of microorganisms and their metabolites in the circulatory system and speed up the onset of cardiovascular diseases ([Battson et al., 2018](#)). Additionally, people with intestinal problems have a higher risk of coronary heart disease even in the absence of usual risk factors ([Rogler and Rosano, 2014](#)). Therefore, evidence indicates that there is a bi-directional communication network between the intestine and cardiovascular, namely, the “gut-cardiovascular axis” ([Table 7](#)).

Increasing data indicate that the pathophysiology of heart failure implicates the stomach. The available evidence shows that SCFA are quickly taken and oxidized by the heart to provide energy for the heart and prevent heart failure ([Palm et al., 2022](#)). For example, due to factors such as decreased microbiota diversity, fewer

butyrate-producing strains, and the fact that SCFA are mainly produced in vivo by microorganisms, patients with heart failure have a limited capacity to create SCFA overall ([Jin et al., 2021](#)). Acetate extraction in the heart failure cohort increased by about 20%, according to a study showing that although the contribution of SCFA to cardiac ATP synthesis was relatively low. This result suggested that increasing SCFA levels in circulating system may benefit energy production in heart failure patients ([Murashige et al., 2020](#)). Surprisingly, it has been reported that in healthy and failing hearts, ATP synthesis from butyrate was significantly higher than that from ketone bodies, indicating that SCFA are more effective energy generators ([Carley et al., 2021](#)).

Hypertension is considered the main risk factor of cardiovascular disease, which is influenced by genetics and environment. The high prevalence rate of hypertension has made it a major global health challenge ([Mills et al., 2020](#)). Research has revealed that

SCFA produced by dietary fiber under anaerobic fermentation of gut microbiota was involved in the regulation of blood pressure (Forkosh and Ilan, 2019; Yang et al., 2020a). According to a review, blood pressure can be impacted by even a very low concentration of SCFA in the gut (Yang et al., 2020a). Acetate supplementation has been confirmed to have beneficial effects on reducing the development of hypertension in obstructive sleep apnea and a hypertensive mice model (Ganesh et al., 2018; Marques et al., 2017; Poll et al., 2021). Propionate intervention may lower blood pressure by regulating Treg cells to reduce systemic inflammation in mice (Bartolomaeus et al., 2019). The possibility of GPR receptors in vascular tissues as well as olfactory receptor 78 as the mechanism through which propionate reduces blood pressure has been considered (Natarajan et al., 2016). G-protein coupled receptor receptors are thought to be vital effectors in regulating blood pressure induced by SCFA (Miyamoto et al., 2016; Zhang et al., 2022b). Exogenous SCFA were found to lower blood pressure, and GPR41/43 inhibitors could attenuate these effects (Onyszkiewicz et al., 2020). The GPR41/43 receptors and colonic vagus nerve signaling were engaged in butyrate's ability to inhibit the onset of hypertension (Onyszkiewicz et al., 2019). Compared with wild-type rats, salt-sensitive *Gper1*^{-/-} rats had lower blood pressure and fewer intestinal illnesses, demonstrating that GPER1, one of the GPR receptors, was associated with the regulation of blood pressure (Waghulde et al., 2018). As a bi-directional regulator, hypertension could also disrupt the gut microbiota structure by diminishing its abundance and diversity, thus lowering the concentration of SCFA (Yang et al., 2020a).

Currently, atherosclerosis is considered a chronic inflammatory disease occurring in the large arteries. There is increasing evidence that SCFA may contribute to atherosclerosis. However, different SCFA have various functions in atherosclerosis (Yao et al., 2022). According to the literature, taking a propionate supplement could alleviate atherosclerosis by regulating gut immune system and vascular inflammation (Aguilar et al., 2014; Bartolomaeus et al., 2019; Haghighi et al., 2022). Instead, it is possible to use acetate as the substrate for cholesterol to promote the synthesis of cholesterol (Vourakis et al., 2021).

In summary, the gut-cardiovascular axis is affected by the effects of SCFA on energy production and vascular inflammation, which, in turn, affects cardiovascular function. These outcomes have both beneficial effects (lower incidence of heart failure, hypertension, and atherosclerosis) and pathological effects (induced cholesterol synthesis).

5. Conclusions and perspectives

In conclusion, humans can not only obtain SCFA through microbial fermentation of non-digestible carbohydrates, but also directly through food, especially milk. In addition, the function of the body, including that of the intestine, brain, kidney, liver, lung, and other organs, is significantly influenced by both endogenous synthesis and exogenous supply of SCFA. Through the “gut-organ axes”, SCFA regulate the host's health as a double-edged sword, acting in both positive and negative manner, with the positive effects being more pronounced.

The fundamental processes causing the paradoxical action of SCFA remain poorly understood. Additionally, both their preventive and therapeutic benefits show positive impacts. Several “gut-organ axes” are discussed in the current paper with limitations. For instance, it is not known yet if SCFA affect the “gut-reproductive axis” in any way. What is significantly more crucial is that it is essential to understand how the several “gut-organ axes” that SCFA produce interact with one another. To fully comprehend how SCFA affect organism health and gain new insights into the control and

prevention of the onset of diseases, much needs to be done in the future. Additionally, as for the ruminants, an increasing body of evidence suggests that the supplementation of butyrate enhances the function of the rumen, however, the current knowledge regarding the communication between the intestine and other organs via SCFA still awaits elucidation.

Author contributions

Yanan Gao: Investigation, Resources, Writing-original draft; **Qianqian Yao:** Writing-review & editing; **Lu Meng:** Writing-review & editing; **Jiaqi Wang:** Conceptualization, Funding acquisition; **Nan Zheng:** Conceptualization, Funding acquisition.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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