

Short-Chain Fatty Acids: A Comprehensive Review On Balancing Health Benefits And Risks In Metabolic Disorders

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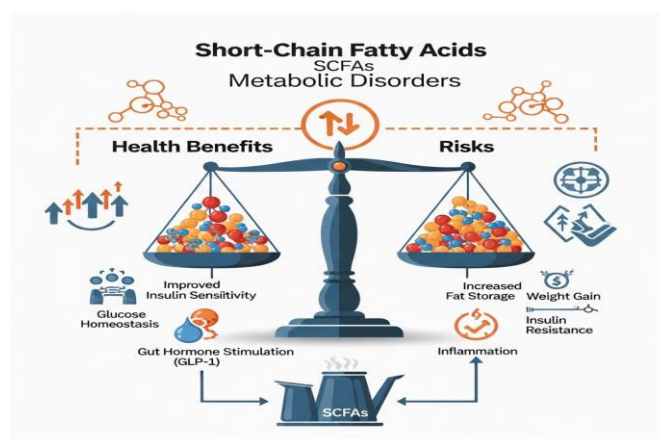
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ABSTRACT

Obesity, diabetes, and other metabolic disorders are among the many diseases that are mostly regulated by short-chain fatty acids [SCFAs]. SCFAs, which are mostly formed by the gut microbiota fermenting dietary fiber, have both positive and negative health consequences. Their role in energy balance and adipose tissue metabolism, which affects insulin sensitivity, lipid metabolism, and the release of hunger-controlling hormones like ghrelin and leptin, makes them crucial in obesity. However, increased levels of SCFA, especially acetate and propionate, may lead to increased fat storage and weight gain in animal models. SCFAs increase insulin secretion and glucose absorption, which improves glucose homeostasis and insulin sensitivity in the treatment of diabetes via stimulating gut hormones like GLP-1. Conversely, high butyrate levels have been linked to inflammation and insulin resistance. In addition to metabolic issues, SCFAs influence the development of cardiovascular diseases, colon cancer, and inflammatory bowel disease through the control of immune responses and gut inflammation. Therefore, abnormalities in the synthesis of SCFAs may have adverse effects even if they have the potential to be metabolic modulators. This highlights the need for additional study to elucidate their mechanisms and enhance therapeutic strategies that focus on the gut microbiota's activities. A feasible route to improved management and preventative strategies is provided by the complex link between SCFAs and illness.

Key-words: SCAs, Gut Microbiota, Metabolic Disorders, Type 2 diabetes, Insulin sensitivity, Obesity

Graphical Abstract:



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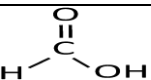
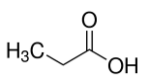
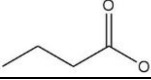
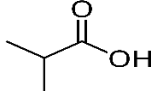
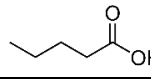
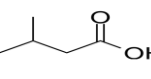
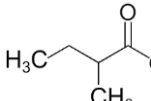
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1. INTRODUCTION

The gut microbiota ferments indigestible food fiber to create SCFAs, mainly butyrate, propionate, and acetate. Because of their anti-inflammatory properties, short-chain fatty acids may help your body in a variety of ways, including chronic conditions including intestinal disorders, immunological problems, and diabetes, obesity, and neurodegenerative diseases. Therefore, maintaining your good gut flora can be a smart investment. SCFAs are small, volatile, aliphatic carboxylic acids containing one to five carbon atoms, as seen in Table 1 [3].

Table 1: SCFA containing 1-5 carbon atoms [3]

Carbon Number	Common Name	IUPAC Name	Common Anion	IUPAC Anion	Chemical Structure
1	Formic acid	Methanoic acid	Formate	Methanoate	
2	Acetic acid	Ethanoic acid	Acetate	Ethanoate	
3	Propionic acid	Propanoic acid	Propionate	Propanoate	
4	Butyric acid	Butanoic acid	Butyrate	Butanoate	
4	Isobutyric acid	2-Methylpropanoic acid	Isobutyrate	2-Methylpropanoate	
5	Valeric acid	Pentanoic acid	Valerate	Pentanoate	
5	Isovaleric acid	3-Methylbutanoic acid	Isovalerate	3-Methylbutanoate	
5	2-Methylbutyric acid	2-Methylbutanoic acid	2-Methylbutyrate	2-Methylbutanoate	

Acetate, propionate, and butyrate are the most common SCFAs in the human body [$> 90\%$] and are found in the colon and feces in a molar ratio of about 60:20:20 [1]. The human gut's concentration of SCFAs varies, with the cecum having high concentrations, the descending colon having intermediate quantities, and the terminal ileum having low concentrations [2].

1.1 SCFAs' Origin and Purpose

Saturated fatty acids with a chain length of one to six carbon atoms are known as SCFAs. The SCFAs that are most common in the intestine are butyrate, propionate, and acetate. SCFAs affect several cell types and regulate important biological processes such as intestinal function, immunology, and host metabolism [9, 10, 11, 7, 8]. Acetate, propionate, and butyrate have a molar ratio of about 60:20:20 in the human colon and feces.

Each SCFA is produced by bacterial fermentation. Therefore, the main reason for the different levels of acetate, propionate, and butyrate was the catabolism of the different bacteria [12]. Cross-feeding with bacteria that generate acetate [*Akkermansia muciniphila*] and butyrate [*Faecalibacterium prausnitzii*] can increase gut SCFA levels and has beneficial preventative and therapeutic effects on inflammation and malignancies [13].

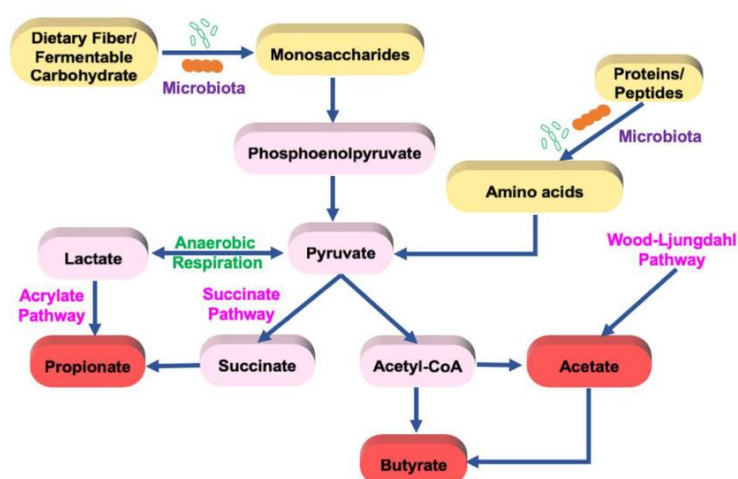


Figure 1: Schematic representation of the fermentation pathways for carbohydrates that provide butyrate, propionate, and acetate

Table 2: Sources of acetate, propionate, and butyrate

S.No	SCFAs	Origin
1	Acetate	Akkermansia muciniphila, Bacteroides spp., Bifidobacterium spp., Prevotella spp., Ruminococcus spp., Escherichia coli, Blautia hydrogenotrophica, Clostridium spp., and Streptococcus spp
2	Propionate	Bacteroides uniformis, Bacteroides vulgatus, Prevotellacopr, Alistipes putredinis, Roseburia inulinivorans, Eubacterium hallii, Blautiaobeum, Coprococcuscatus, Dialisterinvisus Phascolarctobacterium succinatutens, Akkermansia muciniphila, Dialister spp., Veillonella spp., Megasphaera elsdenii, Coprococcuscatus, Bacteroides spp., Salmonella spp., Roseburia inulinivorans, and Ruminococcus obeum
3	Butyrate	Clostridium clusters IV and XIVa, Faecalibacterium prausnitzii, Ruminococcus bromii, Lachnospiraceae, Eubacterium rectale, Roseburia spp., Roseburia inulinivorans, Roseburia intestinalis, Eubacterium hallii, Anaerostipes hadrus, Anaerostipes spp., Coprococcus eutactus, Coprococcus comes, Coprococcuscatus, Subdoligranulum variabile, Eubacterium bifforme, Actinobacteria, Fusobacteria, Spirochaetes, and Thermotogae

1.1.1 Propionate

Propionate is mostly formed from carbohydrate metabolism during glycolysis, mainly by the succinate route, as indicated by the widespread distribution of the methylmalonyl-CoA decarboxylase [mmdA] gene in Bacteroidetes and several Negativicutes [Fig 2]. Bacteroides and gram-negative bacteria, such as A. muciniphila and Roseburia inulinivorans [Table 1], are frequently responsible for human coliforms [14, 15, 30]. Propionate in hens has been demonstrated to reduce fat deposition in vitro, block hepatocyte adipogenesis, and increase the production of glucagon-like peptide-1 [GLP-1] by IECs [31]. These microorganisms contribute to maintaining human health.

Propionate also contributes to liver gluconeogenesis in rats by blocking hydroxy-methylglutaryl-CoA reductase, which inhibits the liver's ability to synthesize cholesterol [3-hydroxy-3-methylglutaryl-CoA, HMG-CoA] [32]. Propionate, a GPR41 agonist, targets the enteric nervous system to provide neuroprotection in mice with Parkinson's disease [PD], which is caused by 6-hydroxydopamine. The notion that T cells respond to immunological challenges in the body is further supported by animal research showing that propionate supplementation is either neutral or beneficial for host immune activity against germs and viruses.

Additionally, propionate shields the arteries in NMRI mice by first preventing the immune system's helper T cells from activating and then lowering the cardiovascular system's damage from hypertension. In C57BL/6 J mice, propionate inhibits intestinal cholesterol absorption, reduces the area of aortic atherosclerosis, and regulates dyslipidemia [33]. These findings imply that propionate has significant effects on lipid metabolism, brain function, and cardiovascular diseases. Research has shown that propionate is neutral or beneficial to the host by killing bacteria and viruses, however it is unclear how supplementing with propionate affects immune responses to specific infections.

1.1.2

Acetate

Acetate is mostly produced by anaerobic bacteria that break down dietary fibers in the animal colon. Numerous bacteria, such as *A. muciniphila* and *Bacteroides* species, ferment food to create acetic acid [14, 7, 15, 16, 17]. Acetyl-CoA is the main byproduct of glycolysis and is then converted to butyrate by the enzyme butyryl-CoA:acetyl-CoA transferase [Fig. 1] [14]. This fermentation product, which is either absorbed by intestinal epithelial cells [IECs] or later transported to the bloodstream by the intestinal epithelium before being quickly absorbed by the liver through the hepatic portal vein, is most concentrated in the proximal colon [18, 19].

Acetate maintains energy balance and metabolic homeostasis, suppresses oxidation and mitochondrial stress, affects immunity, controls body weight, and regulates insulin sensitivity by affecting lipid metabolism and glucose homeostasis in both humans and animals [20, 26, 27, 28, 29]. Together, these results suggest that acetate is essential for weight control, lipid metabolism, tumor growth, and neurological diseases. However, additional research is needed to determine the precise metabolic differences in acetate utilization and to look into the mechanisms via which acetate functions in these conditions.

1.1.3 Butyrate

Many commensal bacteria, including as *Clostridium* clusters IV and XIVa and *F. prausnitzii*, promote the production of butyrate, which is subsequently absorbed by human host IECs [Table 1] [15]. Colonocytes need butyrate, a major metabolite of gut bacteria, to sustain their energy supply [2]. To create butyrate from carbohydrates, two acetyl-CoA molecules join to produce acetoacetyl-CoA, which is subsequently progressively reduced to butyryl-CoA. This process is known as glycolysis.

The final stage of butyrate generation from butyryl-CoA is accomplished by either the phospho-butyrate and butyrate kinase pathways or the butyryl-CoA:acetate CoA-transferase pathway [Fig. 1] [16]. Butyrate repairs the epithelial barrier of the airway by inhibiting the synthesis of interleukin [IL]-6 and lowering the expression of IL-4 and zonula occludens protein 1 [ZO-1] in 16HBE human bronchial epithelial cells. This results in the phosphorylation of extracellular signal-regulated protein kinase 1/2 [ERK1/2] and c-Jun N-terminal kinase [JNK] [34].

Malignant colon cells use glucose as their main energy source due to the Warburg effect, whereas normal IECs use butyrate. Butyrate accumulates and inhibits HDAC, preventing the proliferation of HCT116 colon cancer cells. Butyrate helps the colonic mucosa of BALB/c mice stay intact, prevents colitis, and prevents the onset and spread of cancer via regulating cell proliferation, apoptosis, and differentiation [2]. In animals with intestinal diseases, butyrate improves intestinal barrier function and lowers intestinal inflammatory responses via interacting with GPCRs and inhibiting HDACs. These findings imply that butyrate lowers colonic inflammation and stops colon cancer from developing and spreading, mainly via enhancing the integrity of the intestinal barrier [35].

2. SCFA PRODUCTION IN THE BODY

Gut microbiota are responsible for producing the generation of SCFAs and rely on dietary macronutrient composition including consumption of fiber, composition of anaerobic microorganisms, and host features Fig. 2 shows the production of SCFAs. [3]

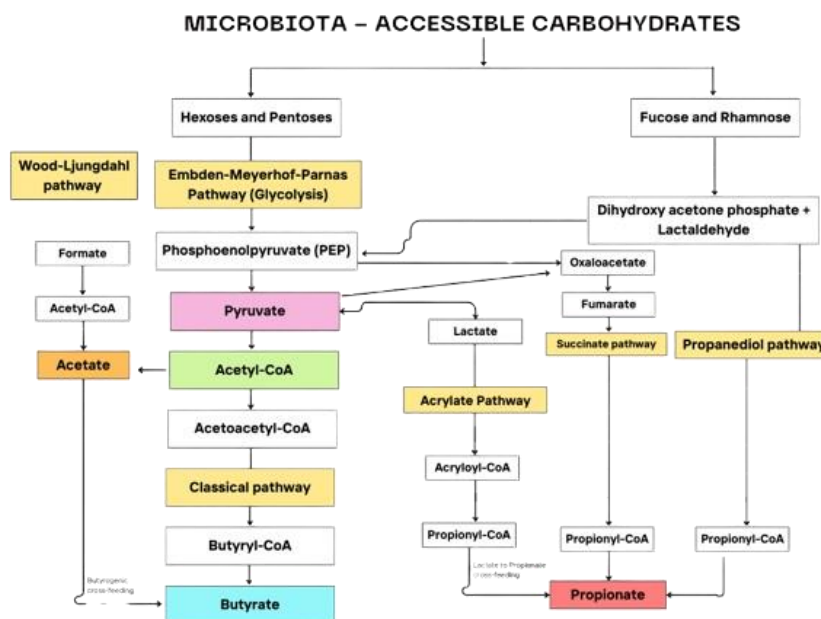


Figure 2: SCFA biosynthesis through bacterial cross-feeding and carbohydrate fermentation [3].

3. SCFAS' TRANSPORT WITHIN THE BODY

Three different kinds of transporters carry the SCFAs into the bloodstream after they are produced in the intestine:

- SCFA-bicarbonate co-transporter component
- Transporters of mono-carboxylate [MCT] 1-4; furthermore, transport pyruvate and lactate.
- Mono-carboxylate transporter that is dependent on sodium [SMCT, SLC5A8]. Although it also transports propionate and acetate, SMCT1 prefers butyrate. [4]

Acetate is the most common SCFA in the gut and blood. There is a significant concentration differential between the intestinal lumen and blood. Colocyte transporters may be rate-limiting for the metabolism of SCFAs, especially propionate and butyrate, as intestinal uptake seems to be slower than colonocyte metabolism or blood evacuation. [5]

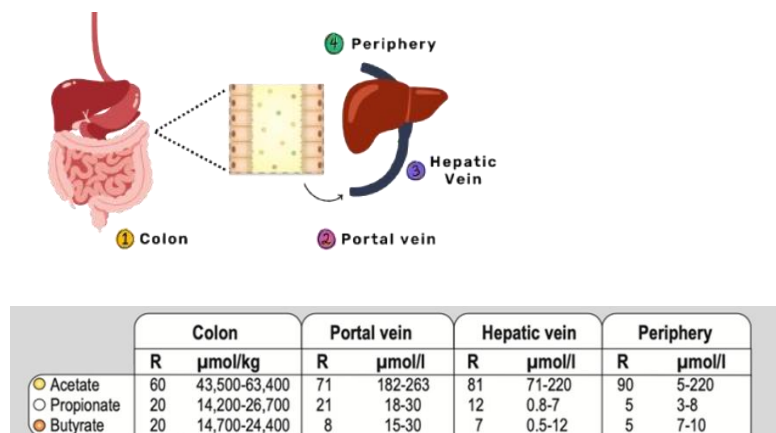


Figure 3: SCFAs molar ratio [R] and concentration [5].

4. RECEPTORS FOR SCFAS:

GPCRs are the largest type of receptors present in mammals, with seven transmembrane domains. These receptors control almost all physiological functions of cells in vivo. Lipids, carbohydrates, chemokines, hormones, and neurotransmitters are among the materials in the extracellular environment that GPCRs can bind to. GPR41 and GPR43 are thought to be the most important SCFA receptors in the GPCR family.

A recent study found that SCFAs can also activate GPR109A. GPR109A, unlike GPR41 and GPR43, is activated by longer SCFAs, mainly C4. A number of SCFA receptors have different affinities. In humans, the affinity rating for GPR41 is $C3 = C4 = C5 > C2 > C1$, whereas the affinity rating for GPR43 is $C2 = C3 > C4 > C5 = C1$. GPCRs have reportedly been connected to metabolic diseases, neurological conditions, cardiovascular disease, cancer, and inflammation. GPCRs have therefore drawn attention as potential therapeutic targets for a variety of diseases [36,37,38,39].

4.1 GPR109A

Butyrate and β -hydroxybutyrate activate GPR109A, which was first identified as a nicotinic acid receptor. Acetate and propionate do not activate it. GPR109A is a Gi/o coupling protein expressed by colonic epithelial cells. The protein is downregulated in mice that are germ-free. Butyrate inhibits osteolysis in mice and stops titanium particle-induced activation of the NLR family pyrin domain containing 3 [NLRP3] inflammasome by activating its receptor GPR109A. Obese mice given butyrate demonstrated improved glucose metabolism and decreased adipose tissue inflammation through GPR109A activation.

Thus, blocking GPR109A may be a unique way to treat obesity by lowering metabolic and inflammatory dysfunctions. In C57BL/6 mice, butyrate-activated GPR109A increases the anti-inflammatory capacity of colon macrophages and dendritic cells, inhibits colon inflammation and carcinogenesis, and promotes the growth of Tregs and IL-10-producing T cells. The combined findings demonstrate that GPR109A is expressed in a range of organs and cells and is beneficial for metabolism and immunity. The mechanism requires further investigation [46, 47, 48].

4.2 GPR41

GPR41 is a Gi/o-coupled receptor for SCFAs and binds to ligands like butyrate [C4], propionate [C3], and acetate [C2]. Recent studies have shown that SCFAs produced by microbial fermentation bind to receptors, such as GPR41, to act as signaling molecules. Thus, the gut microbiota affects host physiological and pathological processes through these receptors. Exogenous SCFA treatment reduces liver fat content and improves liver metabolism in GPR41^{-/-} mice by inhibiting the expression of lipid production genes. GPR41 is necessary for propionate to decrease allergy inflammation, although GPR43 is not.

Mice's bone marrow hematopoietic activity alters when propionic acid therapy activates GPR41. Increased macrophage and dendritic cell precursor synthesis, followed by the implantation of highly phagocytic dendritic cells in the lungs, are the hallmarks of this condition. These cells mold the immunological milieu in the lungs and affect how severe allergic inflammation is. Additionally, SCFAs reduce inflammation and maintain intestinal homeostasis by stimulating human CD4⁺T and innate lymphoid cells to synthesize IL-22 through GPR41. Consequently, GPR41 is a SCFA receptor that is important in immunological, metabolic, inflammatory, and other diseases and deserves further study [40, 41, 42].

4.3 GPR43

GPR43 is activated by butyrate [C4], propionate [C3], and acetate [C2] [80]. The Gi/o- and Gq double-coupled receptor GPR43 is expressed by intestinal endocrine cells, including L cells [84]. GPR43 is also present in immune cells like monocytes, neutrophils, eosinophils, and regulatory T cells [Tregs]. GPR43^{-/-} mice IECs show decreased expression of regenerating islet-derived protein 3 gamma [RegIII γ] and β -defensin. In wild-type mice, oral SCFA administration maintains intestinal homeostasis by inducing the production of antimicrobial peptides by the signal transducer and activator of transcription 3 [STAT3] and mammalian target of rapamycin [mTOR] pathways in IECs.

GPR43 activation reduces kidney damage in animal models of type 2 diabetes and diabetic nephropathy brought on by streptozotocin and high-fat diet [HFD], enhances the interaction between β -arrestin-2 and I- κ B α , and

inhibits oxidative stress and nuclear factor- κ B [NF- κ B] activation brought on by hyperglycemia. By inhibiting GPR43, short interfering RNA lessens this effect in mouse glomerular mesangial cells. Mice without GPR43 develop obesity under typical dietary conditions, but mice with specialized adipose tissue expression of GPR43 remain slender even when fed a high-fat diet.

SCFA-mediated GPR43 activation promotes the metabolism of fat and glucose in other tissues while preventing fat accumulation in adipose tissue via inhibiting insulin signaling in adipose cells. These findings suggest that GPR43, which functions as a sensor of excess dietary energy, controls energy consumption and maintains metabolic balance. GPR43, which is essential for several physiological functions, is expressed by islet cells, adipose tissue, and the digestive tract. [40, 43, 44, 45].

5. SCFA'S PHYSIOLOGICAL FUNCTION IN METABOLIC CONDITIONS:

5.1 SCFAs and Diabetes:

SCFAs are known to prevent diabetes by activating metabolite-sensing GPCRs, including GPR43, on enteroendocrine-producing cells and pancreatic β cells, which are crucial for glucose tolerance [62]. The preventive effects of SCFAs against type 1 diabetes [T1D] have been studied mechanistically using non-obese [NOD] mice. Compared to NOD animals with diabetes, mice without diabetes had substantially higher peripheral blood levels of SCFAs. Germ-free mice were more likely to develop T1D than normal mice, suggesting that microbiota contributes to the suppression of T1D. Mice who were fed acetate-containing drinking water also had a lower incidence of T1D. Acetylated or butyrate resistant starches were more successful at lowering T1D than SCFAs administered through drinking water.

Thus, high-fiber diets and the microbiome may cooperate to lower the incidence of T1D in susceptible individuals [57]. The suppression of T1D development by fecal transfer of the larger bacteria into NOD recipients [64] indicates that a change in the bacterial composition is necessary for SCFA-mediated T1D protection. Butyrate and acetate-containing diets reduced the quantity of autoreactive T cells in lymphoid tissue and the expression of CD86 in mature marginal-zone B cells, a sub-assembly that is implicated in the pathogenesis of autoimmune disorders and produces IL-12. While acetate was more successful at suppressing T1D, butyrate and propionate were more effective at producing T regs, most likely because to their HDAC inhibition action [61, 63].

Butyrate enhances the formation of regulatory T cells by increasing histone H3 acetylation in the Foxp3 locus promoter and the conserved non-coding sequence area. In order to protect pancreatic β cells and enteroendocrine-producing cells, which are crucial for glucose tolerance, from type 1 diabetes, SCFAs may contribute to the activation of metabolite-sensing GPCRs [57]. Because obese and type 2 diabetic patients showed considerably lower levels of gut microbial diversity and GPR41 promoter region methylation than lean individuals, there is a correlation between a higher body mass index and lower levels of GPR41 methylation [61, 65].

Unbalanced blood sugar and cholesterol levels are hallmarks of type 2 diabetes. About 90% of cases of diabetes globally are caused by an imbalanced gut microbiota, which also contributes to the quick development of type 2 diabetes insulin resistance. According to reports, T2D patients have higher levels of Proteobacteria and a higher Firmicutes/Bacteroidetes ratio than healthy individuals, but Bacteroides, which produce SCFA, are less common. Patients with type 2 diabetes have significantly dysregulated levels of lipids, bile acids, and SCFAs. A growing body of research has demonstrated the critical functions SCFAs play in restoring insulin sensitivity.

On the surface of rat intestinal cells, acetate and butyrate activate GPR43 and GPR41, which encourages the release of insulin, GLP-1, and peptide YY. This lowers peripheral blood glucose levels and controls blood lipid energy metabolism. While anomalies in the generation or absorption of propionate are causally linked to an increased risk of type 2 diabetes, an increase in gut butyrate production caused by the human genome is linked to an enhanced insulin response following an oral glucose tolerance test. Probiotics improve insulin production through GLP-1 secretion driven by glucose, activate the phosphoinositide 3-kinase [PI3K]/AKT pathway to prevent pancreatic cell apoptosis, and raise the activity of GPR43/41, proglucagon, and proconvertase 1/3.

By raising GPCR levels and encouraging the production of insulin, GLP-1, and peptide YY, the results demonstrate that SCFAs can lower peripheral blood glucose levels and ameliorate insulin resistance [Fig. 6]. It is unknown, therefore, what dosages and permissible exposure durations are appropriate for treating T2D with SCFA. Furthermore, it is still unknown if SCFA administration has time- or dose-dependent effects.

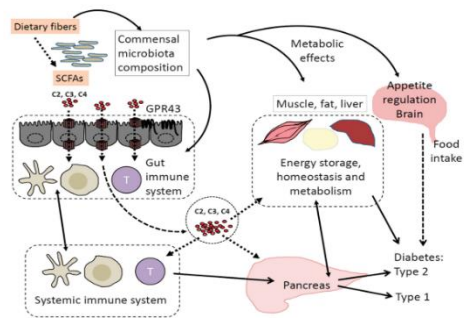


Figure 4: Benefits of DF and SCFAs for diabetes

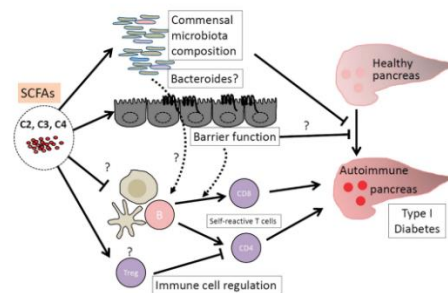


Figure 5: Suppression of T1D by SCFAs.

5.2 SCFAs and Obesity

The main SCFAs produced by colonic anaerobic bacteria are acetic acid [C2:0], propionic acid [C3:0], and butyric acid [C4:0] [49, 50]

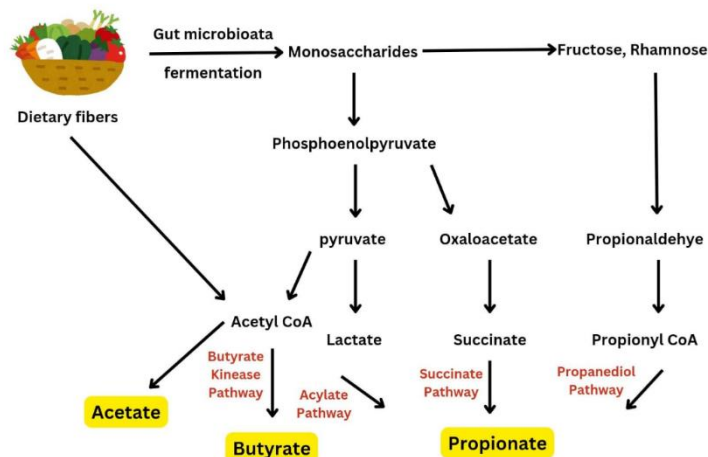


Figure 6: Pathways for the biosynthesis of short-chain fatty acids by gut microbiota.

Recent research indicates that SCFAs are essential for human health. Supplementing with dietary fiber has been shown to help reduce body weight, insulin resistance, and dyslipidemia—metabolic markers associated with obesity [51, 52]. Human investigations have confirmed the molecular basis of SCFA receptor-mediated metabolic responses by demonstrating that administering propionate to obese patients increased PYY and GLP-1 production and secretion while reducing adiposity and overall weight gain [53,54]. Butyrate has received a lot of attention lately since it seems to have a significant role in the development of diabetes and obesity. Propionate and butyrate

may promote metabolic health by encouraging intestinal gluconeogenesis [IGN]. This activation allowed for the explanation of the dietary fibers' anti-obesity and antidiabetic properties.

IGN activation by propionate was assumed to be mediated by the gut-brain axis including GPR41, while butyrate and propionate could directly stimulate the expression of IGN genes through a cAMP-dependent route [55]. Butyrate promotes mitochondrial biogenesis and fatty acid oxidation via the adiponectin-mediated AMPK pathway by inhibiting histone deacetylases [HDACs] and increasing peroxisome proliferator-activated receptor alpha [PPAR α] [56,57]. These all demonstrated how SCFAs regulate the epigenome by altering HDACs and acting as signaling molecules. Butyrate-activated GPR109a has been shown to induce lipid homeostasis by promoting the formation of local macrophages in adipose tissue.

GPR109a, which is expressed in human isolated β cells, was down-regulated and prevented insulin from being released in response to glucose stimulation in patients with type 2 diabetes. In contrast, isolated β cells treated with a GPR43-specific agonist boost β cell proliferation, gene expression, and glucose-stimulated insulin production [57]. GPR41 and GPR43, when expressed in adipose tissue, increase the release of leptin and inhibit insulin signaling and adipogenesis, respectively. Acetate and propionate are triggered to produce adipogenicity via GPR43. 58 Therefore, it has been shown that the generation of insulin in pancreatic β cells is directly impacted by SCFA-mediated GPR41/GPR43 signaling. Furthermore, it has been shown that when given a normal diet, genetically modified mice lacking GPR43 are overweight.

Propionate stimulates the sympathetic nervous system, which helps control body weight. Additionally, when SCFAs reduce PPAR α expression, oxidative metabolism in the liver and adipose tissue increases, hepatic steatosis and body fat accumulation decrease, and insulin sensitivity increases. By encouraging energy expenditure and appetite management, SCFAs have been shown in numerous studies to help prevent obesity [59]. Other studies suggest that obesity may be associated with higher levels of SCFAs in the feces. However, SCFA dietary supplements can prevent overweight individuals from gaining weight as a result of eating a high-fat diet; these supplements caused significant changes in GPR43 and GPR41 expressions, which were marked by decreases in colon and increases in adipose tissue.

Studies have shown that obesity and high-carb diets may reduce the binding of SCFAs to GPCRs, which are signal transduction molecules that may improve hepatic lipogenesis and intestinal energy absorption [60]. Furthermore, unlike obesity, dietary SCFAs have an impact on the makeup of the bacterial population in feces, increasing the proportion of Bacteroidetes and decreasing the number of Firmicutes [55]. Globally, reducing body weight is associated with enhanced beige adipogenesis, mitochondrial biogenesis, and adipose tissue triglyceride hydrolysis and free fatty acid oxidation [53]. Further investigation into SCFAs and their receptors may open up new treatment options for obesity and associated health risks by either enhancing or suppressing SCFA signaling, in addition to their potential as epigenetic modulators.

Gut dysbiosis may be associated with elevated amounts of SCFAs in the feces [60]. Certain bacterial components connected to the latter have been implicated in the development of obesity and other metabolic diseases. These components have altered the gut microbiota and caused low-grade inflammation in adipose tissue. Because they may also contribute to the pathophysiology of obesity, SCFAs may have a significant effect on obesity-related diseases like type 2 diabetes mellitus [T2DM] by influencing body weight control through effects on energy expenditure, energy intake, systemic low-grade inflammation, and insulin sensitivity [61].

Table 3: Results of studies on the administration of SCFAs in obesity and obesity-related diseases

Administration	Model	Effect on Obesity Control
Isobutyrate, isovalerate	Primary adipocytes	Lipolysis, lipogenesis, insulin-stimulated glucose uptake
Acetate, propionate, butyrate	NCI-H716 and HuTu-80 cells	PYY expression
Butyrate	Caco-2/TC-7 cells	Gut barrier integrity

Administration	Model	Effect on Obesity Control
Butyrate	Caco-2 cells and peripheral blood cells	IL-10 secretion
Butyrate	Cancer cells	Apoptosis
Propionate, butyrate	Cancer cells	Cholesterol and very-low-density lipoprotein secretion
Acetate, butyrate	Rat colon	PYY and GLP-1 secretion
Butyrate	Mice and RAW 264.7 macrophages	Anti-inflammatory response
Propionate	Human colonic cells	Enhanced GLP-1 secretion, resting energy expenditure
Acetate, propionate, butyrate	C57BL/6 J mice	Body weight gain, plasma free FAs, TGR5/GPCR expression, physical activity, inflammation, working memory
Butyrate	C57BL/6 J mice	Inflammation
Butyrate	Germ-free mice	Body weight gain, adiposity, gut barrier integrity
Butyrate	C57BL/6 J mice	Body weight gain, adiposity
Butyrate	C57BL/6 J mice	Increased intestinal gluconeogenesis, FA oxidation, thermogenesis, energy expenditure
Acetate, butyrate, propionate	C57BL/6 J mice	PYY and GLP-1 secretion
Butyrate	Human white adipose tissue	Body weight and fat deposition
Acetate, propionate, butyrate	C57BL/6 J and Ucp1 ^{-/-} mice	Plasma cholesterol
Butyrate	C57BL/6 J and 129/SvR mice	Body weight and fat deposition
Acetate, propionate, butyrate	Wistar/ST rats	Plasma cholesterol
Acetate	Human	Fat oxidation, inflammation, PYY secretion, post-prandial insulin secretion

6. OTHER THERAPEUTIC USES OF SCFA'S:

6.1. NAFLD

The gut-liver axis, a reciprocal relationship between the gut and its microbiota and the liver, is the outcome of the integration of signals produced by dietary, genetic, and environmental variables [70]. This mutually advantageous relationship is established by the portal vein, which transports gut-derived products directly to the liver and serves as a feedback route for bile secretion into the intestine [71]. Microbe-produced metabolites such as ethanol, trimethylamine, secondary bile acids, and SCFAs have been shown to have a pathogenic role in the development of non-alcoholic fatty liver disease (NAFLD) [73].

While acetate acts as a substrate for hepatic fat synthesis, which promotes the creation of fat, propionate, which is significant in NAFLD patients, alters liver metabolism and reduces lipid storage [72,73]. By inhibiting HDAC-2, butyrate supplementation increases the expression of the GLP-1 receptor in the livers of NAFLD mice, promoting energy metabolism and preventing fat accumulation. NAFLD patients' livers exhibit a substantial downregulation of the GLP-1 receptor. [70–73]

6.2. IBD

IBD is an idiopathic intestinal inflammatory disease that affects the colon, rectal area, and ileum. It is also referred to as ulcerative colitis and Crohn's disease. [66] Repeated cycles of epithelial damage, inflammatory cell infiltration into the lamina propria, and immune regulation failure to control the inflammatory response—which

leads to recurrent cycles of chronic inflammatory remission and relapse in the gastrointestinal tract—are characteristics that set apart both IBD subtypes. [67] IBD is closely associated with a disruption in the gut flora. IBD patients have significantly lower levels of SCFA-producing bacteria, such as *F. prausnitzii* and *Roseburia intestinalis* [67, 68, 69].

Their reductions make it more difficult for bacteria and immune cells to communicate. Patients with IBD have significantly reduced levels of acetate and propionate in their intestinal lumen. [69] Because SCFAs control the innate and adaptive immune cells' generation, activity, and trafficking—all of which are beneficial in IBD—they have significant immunomodulatory effects. [67] Through the activation of cell surface GPCRs, SCFAs such as acetate, propionate, and butyrate inhibit AKT and NF- κ B. By blocking the NF- κ B p65 signaling pathway, 2,4,6-trinitrobenzene sulfonic acid [TNBS]-induced colon inflammation is reduced. Through the use of GPCRs on the cell surface, SCFAs can initiate signaling cascades that modify immune activity and reduce intestinal inflammation. [69]

6.3. Cardio-Protective Activity

Globally, cardiovascular disease, or CVD, is a chronic noncommunicable disease that contributes significantly to morbidity and mortality. [76] The cardiovascular system benefits from SCFAs, and their mechanisms of action are discussed here. [77] By lowering atherosclerosis, SCFAs may safeguard the cardiovascular system.

By lowering intestinal cholesterol absorption through the regulation of related transporter expression, such as ATP-binding cassette [ABC] transporters G5 and G8 and Niemann-Pick C1-like 1 [Npc1l1, a major intestinal cholesterol transporter, butyrate, for instance, was found to slow the progression of diet-induced atherosclerosis. SCFAs have the potential to enhance cardiovascular health and avoid hypertension. [78]. For instance, one study found that acetate had the largest antihypertensive effect among the three SCFAs, butyrate, and propionate, and that they may all lower blood pressure. [79]

6.4. CKD

Reduced renal function in CKD leads to uraemic toxin accumulation in the colon, which changes the makeup of bacteria and metabolites in the feces. [74] The prognosis of chronic kidney illness is impacted by positive feedback, which happens when changed metabolites permit endotoxins to enter the bloodstream and increase local kidney inflammation. SCFAs, especially propionate, decrease p38 and JNK phosphorylation in human renal cortical epithelial cells, which in turn decreases TNF- α -induced monocyte chemotactic protein-1 production. This lessens kidney fibrosis and inflammation. [75]

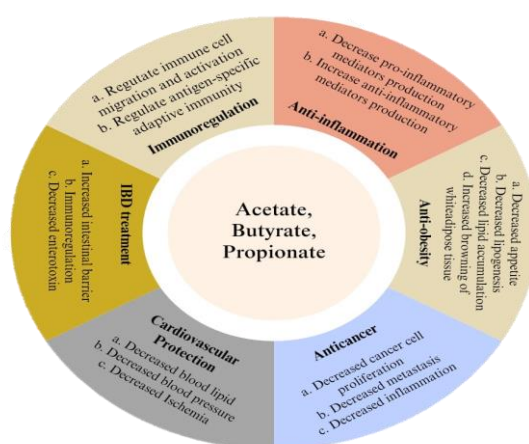


Figure 7: Health advantages and the linked processes of SCFAs. The symbols ↓ and ↑ stand for decline and rise, respectively.

CONCLUSION:

The involvement of short-chain fatty acids [SCFAs] has been shown to be important in a variety of diseases, such as diabetes, obesity, and other metabolic conditions. The fermentation of dietary fiber by gut bacteria is the primary source of SCFAs, which have been shown to have both positive and negative effects on human health. Adipose tissue metabolism and energy balance modulation have demonstrated the relevance of SCFAs in obesity. They have the ability to affect the release of the hormones ghrelin and leptin, which regulate hunger. They may also affect insulin sensitivity and lipid metabolism. However, it has been demonstrated that higher levels of SCFAs, particularly acetate and propionate, encourage fat deposition and gain in the bodies of rats and mice. It has been demonstrated that SCFAs are highly successful in controlling insulin sensitivity and glucose homeostasis in diabetics. These substances may increase the release of insulin and the tissues' ability to absorb glucose by stimulating gut hormones like GLP-1. Nevertheless, it has also been shown that inflammation and insulin resistance are linked to elevated levels of SCFAs, especially butyrate. In addition, SCFAs have been implicated in the development of cardiovascular disorders, colon cancer, and inflammatory bowel disease. When properly targeted, their effects on the immune system and gut inflammatory responses will either exacerbate or completely eradicate these disorders. Thus, it may be concluded that the role of SCFAs in diabetes, obesity, and other conditions is not that clear-cut.

In another way, these substances may be helpful metabolic modulators. However, problems could arise and result in chronic illnesses if they overproduce or malfunction. Understanding how SCFAs mechanistically affect the onset and course of disease, as well as how therapeutic approaches could alter the production and activity of the gut microbiota to improve disease control, may require more investigation. Deciphering this intricate connection between SCFAs and human health could lead to new developments in disease management and prevention.

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Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Ethics approval and consent to participate

Not applicable. This review article does not involve any studies with human participants or animals performed by any of the authors.

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