Short-Chain Fatty Acids

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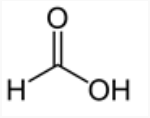
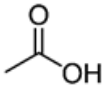
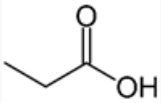
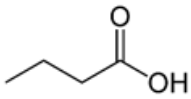
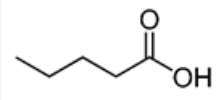
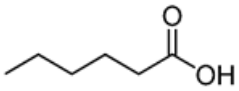
The relationship between diet and the diversity and function of the intestinal microbiome and its importance for human health is currently the subject of many studies. The type and proportion
of microorganisms found in the intestines can determine the energy balance of the host. Intestinal microorganisms perform many important functions, one of which is participation in metabolic processes, e.g., in the production of short-chain fatty acids—SCFAs (also called volatile fatty acids). These acids represent the main carbon flow from the diet to the host microbiome. Maintaining intestinal balance is necessary to maintain the host's normal health and prevent many diseases. The results of many studies confirm the beneficial effect of probiotic microorganisms on the balance of the intestinal microbiome and produced metabolites, including SCFAs. The aim of this review is to summarize what is known on the effects of probiotics on the production of short-chain fatty acids by gut microbes. In addition, the mechanism of formation and properties of these metabolites is discussed and verified test results confirming the effectiveness of probiotics in human nutrition by modulating SCFAs production by intestinal microbiome is presented.

Organic acids, principally the short-chain fatty acids (SCFAs) are formed in the GI tract in millimolar quantities and especially occur in high amounts in those areas where anaerobic microorganisms are predominant. SCFAs are volatile saturated fatty acids that have in their chain 1-6 carbon atoms in the aliphatic chain, existing in a straight or branched conformation [1]. In this review, attention has been focused on SCFAs with a simple conformation, which include formic, acetic, propionic, butyric, valerian, and caproic acids (Table 1).

Table 1. Chemical and structural formulas of short-chain fatty acids (SCFAs) [2].

Name	Chemical Formula	Structural Formula	Molar Mass [g/mol]
Formic acid	HCOOH		46.03
Acetic acid	CH_3COOH		60.05
Propionic acid	CH_3CH_2COOH		74.08
Butyric acid	$CH_3(CH_2)_2COOH$		88.11
Valeric acid	$CH_3(CH_2)_3COOH$		102.13

Caproic acid	$CH_3(CH_2)_4COOH$		116.16

SCFAs represent the main carbon flow from the diet to the host microbiome [3]. The formation of these acids is relatively well-known and described [4][5]. The concentration and ratio of resulting SCFAs depend not only on the composition of the microbiome and the number of individual microorganisms in the colon, but also on the type of dietary fibers supplied to the microorganisms as a substrate in the fermentation process, and thus on the diet [6]. The most common are acetic acid, propionic acid and butyric acid (in a 3:1:1 molar ratio), which constitute 90%–95% of SCFAs present in the human colon, while a smaller proportion of these is formic acid [1].

In addition, the fermentation of selected, often rapidly fermentable non-digestible carbohydrates (NDCs) produces another organic acid-lactic acid [3]. Although it does not belong to the group of SCFAs, this acid can be produced by lactic acid bacteria, e.g., the genera *Lactobacillus* and *Bifidobacterium* [5]. However, under normal conditions it is not accumulated in the colon due to the presence of some bacterial species, e.g., *Eubacterium hallii*, that can convert lactate into different SCFAs [5]. Metagenomic analyses have greatly facilitated the identification of the types of bacteria responsible for the production of SCFAs and lactic acid (Table 2).

Table 2. Examples of commensal and probiotic microorganisms producing SCFAs and lactic acid [7].

Microorganism/s	Type	Acid/s	References
Bifidobacterium spp., *Blautia hydrogentrophica*, *Prevotella* spp., *Streptococcus* spp.	commensal	acetic	[8]
Akkermansia muciniphilia, *Bacteroides* spp.,	commensal	acetic, propionic	[8][9]
Dalister succinatiphilus, *Eubacterium* spp. (e.g., *E. halli)*, *Megasphaera elsdenii*, *Phascolarctobacterium succinatutens*, *Roseburia* spp., *Salmonella* spp., *Veillonella* spp.	commensal	propionic	[9]
Coprococcus spp. (e.g., *Coprococcus catus*), *Roseburia inulinivorans*	commensal	propionic, butyric	[9][10][11]
Anaerostipes spp., *Coprococcus comes*, *Coprococcus eutactus*, *Clostridium symbiosum*, *Eubacterium rectale*, *Eubacterium hallii*, *Faecalibacterium* spp. (e.g., *Faecalibacterium prausnitzii*), *Roseburia* spp. (e.g., *Roseburia intestinalis*)	commensal	butyric	[8][9][10][11]
Clostridium spp., *Ruminococcus* spp.	commensal	acetic, propionic, butyric	[8][9][11][12]

Bifidobacterium spp.	probiotic	acetic, lactic	[13]
Lactobacillus rhamnosus GG (LGG), *Lactobacillus gasseri* PA 16/8	probiotic	propionic, lactic	[7]
Bifidobacterium longum SP 07/3, *Bifidobacterium bifidum* MF 20/5	probiotic	acetic, propionic, lactic	
Lactobacillus salivarius spp salcinius JCM 1230, *Lactobacillus agilis* JCM 1048	probiotic	propionic, butyric, lactic	[14]
Lactobacillus acidophilus CRL 1014	probiotic	acetic, propionic, butyric, lactic	[15][16][17][18]

Bacterial Fermentation Involved into Production of SCFAs

Endogenous short-chain fatty acids are formed by bacterial fermentation of food fiber and NDCs, which become available to intestinal microorganisms in the large intestine. In addition to resistant starch (RS), plant-derived NDCs include non-starch polysaccharides (NSP), oligosaccharides (prebiotics), oligofructose, disaccharides (lactose, stachyose, raffinose) and monosaccharides e.g., alcohols (sorbitol, mannitol) [19]. There are four types of resistant starch (RS1–RS4) present in the human diet that are resistant to degradation in the small intestine [20][21]. The type of RS has a significant effect on the composition of the intestinal microbiome [22]. In the case of oligosaccharides, particularly important are prebiotics defined as a nonviable food component that confers a health benefit on the host associated with modulation of the microbiota [23]. However, endogenous indigestible carbohydrates include mucin and milk oligosaccharides [19].

Fermentation is an anaerobic redox process in the cytoplasm in which organic compounds are both electron donors and acceptors. In the fermentation process, electrons detached from the oxidized substrate are transferred by NADH directly to the endogenous acceptor. ATP is formed as a result of substrate phosphorylation, with the participation of the corresponding phosphoglycerate, pyruvate, acetate or butyrate kinases. During carbohydrate fermentation, the final electron acceptor is pyruvate or the compounds that are produced from it. The end products of fermentation are various short chain carboxylic acids (e.g., formic, acetic, lactic, butyric, propionic), CO_2, H_2, ethanol, glycerol, acetoin, 2,3-butanediol. Importantly, bacterial growth in populations mixed with other microorganisms can affect the type and amount of products produced during fermentation. The substrates most commonly used by microorganisms in the fermentation process are hexoses and pentoses [24].

Bacteria have a variety of pathways to transform sugars. These sugars are first phosphorylated and then in glycolysis (Embden–Meyerhof–Parnassian pathway), in the Entner–Doudoroff pathway or in the *Bifidobacterium* pathway are transformed into pyruvate or into pyruvate and additional acetyl-phosphate. The Embden–Meyerhof–Parnassian pathway, the major colonic pathway for the catabolism of hexoses, occurs in enterobacteria, clostridia, homofermentative lactic acid bacteria, and propionibacteria, and produces only pyruvate as a partial oxidation product) [25]. The Entner–Doudoroff pathway is used in the fermentation metabolism by e.g., *Zymomonas* (alcoholic fermentation), as well as

Escherichia coli in gluconate fermentation. The *Bifidobacterium* pathway is active in bacteria of the genus *Bifidobacterium*, inhabiting, among others, the human digestive system. Two acetate molecules and one lactate are formed in this pathway. In the phosphoketolase pathway that occurs in heterofermentative lactic acid bacteria or the *Bifidobacterium* pathway, an additional molecule of acetyl-phosphate is generated (Figure 1) [26].

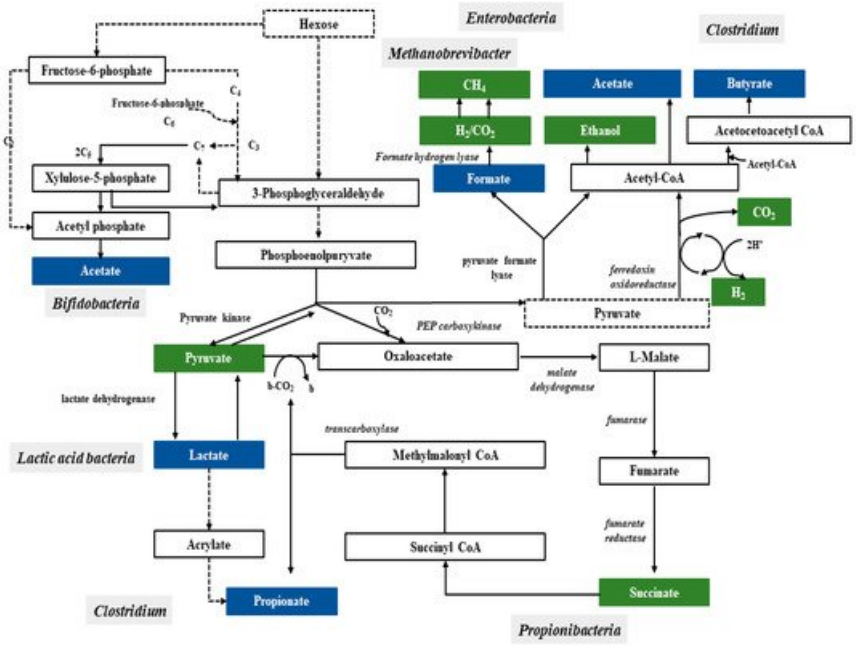


Figure 1. Pathways leading to SCFAs and lactic acid production by intestinal bacteria [25].

In a mixed population such as the intestinal microbiome, carbohydrate breakdown into a mixture of acids involves more than one species. This type of fermentation is called mixed acid fermentation or *Enterobacteriaceae* fermentation and is carried out by some bacteria belonging to this family, including *Escherichia*, *Proteus*, *Salmonella,* and *Shigella* [24]. The fermentation products of some species are substrates for fermentation or incorporated as intermediate metabolites into the metabolic pathways of other species, resulting in substrates being sequentially fermented. Lactate, ethanol, and pyruvate are diminished by subsequent bacterial utilization and SCFAs production. Accordingly, the main final products of sugar catabolism are SCFAs, acetate, propionate and butyrate that account for 85%–95% of total SCFAs in all regions of the colon. Other fermentation end products, such as caproate and valerate, occur in lower amounts [25].

Acetic acid is the most abundant SCFAs in the colon, accounting for more than half of the total SCFAs found in feces [26]. Intestinal microorganisms can produce acetic acid through two major metabolic processes. Most often it is fermentation of indigestible carbohydrates, while about 1/3 of acetic acid is formed as a result of synthesis from hydrogen and carbon dioxide or formic acid by acetogenic bacteria through the Wood–Ljungdahl pathway [4][10].

Some types of *Clostridium* (*C. acetobutylicum*, *C. butyricum*, *C. pasteurianum*, *C. perfringens*) participate in butyric fermentation, as well as e.g., *Butyrivibrio fibrisolvens* and *Fusobacterium nucleatum*. The end products are butyric acid, a small amount of acetic acid and CO_2 and H_2. Some species may also form lactic acid and/or ethanol as well.

For propionic fermentation, the main substrates are glucose and lactate. Its course varies depending on the bacteria; it can occur that it forms succinate or acrylate [24].

Bacteria are capable of fermenting sugar degradation products (glycerol, citrate, malate, succinate, pyruvate, lactate, ethanol, acetate), and a small share of dietary protein fermentation processes in the production of SCFAs has been shown, mainly in the form of acetic and propionic acid [27]. Bacteria of the

genus *Clostridium* are capable of fermenting amino acids. In this process, carbon dioxide, hydrogen, acetate, as well as ammonia and butyrate may form, which have an unpleasant odor. In addition, amino acids such as valine, leucine and isoleucine resulting from the anaerobic breakdown of proteins can be converted into compounds with strong odor, such as isobutyric, isovaleric and hexanoic acids, as well as cadaverine, putrescine, other amines, and hydrogen sulfide and methylmercaptan [24]. Excessive accumulation of isobutyric acid and isovaleric acid indicates a malfunctioning fermentation and digestion processes. These are putrefactive acids, the increased production of which may be associated with an excess of unabsorbed amino acids or proteins reaching the intestines. The possibility of blood in the intestinal contents and the overly intensive development of pathogenic microbiota in the small intestine should also be taken into account, where access to protein compounds is facilitated [28].

Functions of Short-Chain Fatty Acids

SCFAs have been shown to have a very positive effect on the energy metabolism of mammals that use them together with glucose as a metabolic fuel [29]. It has been estimated that the use of SCFAs as an energy source can provide up to 10% of the host's daily calories [30]. The presence of these acids in the human body, mainly acetic, butyric and propionic acids in sufficient quantities is essential for the health and well-being of the host [7]. However, the production of these acids requires the presence of appropriate substrates (dietary fiber and prebiotics) needed for the proper course of the fermentation processes.

SCFAs play a very important role in maintaining intestinal and immune homeostasis in the human body (Figure 2).

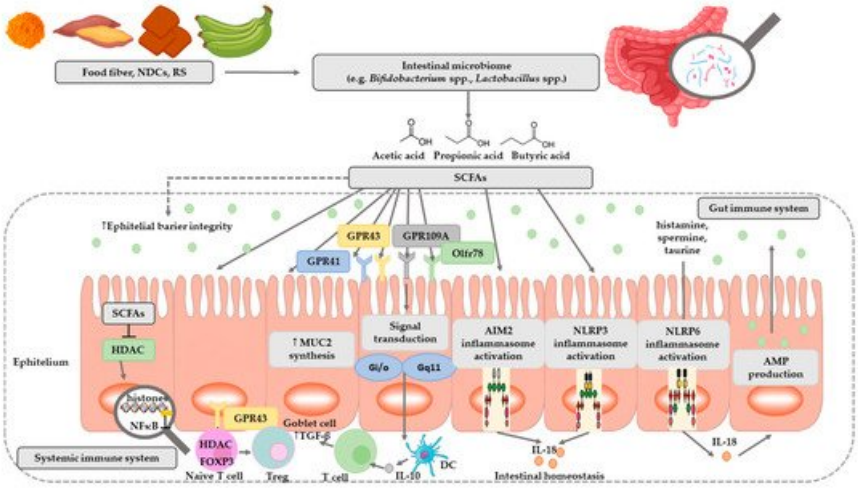


Figure 2. The role of SCFAs in regulation of intestinal homeostasis. SCFAs (acetic, propionic, and butyric acid) are produced by intestinal microbiome in fermentation of undigested food fiber, non-digestible carbohydrates (NDCs) or resistant starch (RS). SCFAs are as energy substrates for colonocytes and regulate intestinal barrier function (synthesis of mucin-MUC2) and immune system through G-protein-coupled receptors (GPR41, GPR43, GPR109A) and Olfr78 receptor signaling. SCFAs regulate the histone deacetylase (HDAC) activity which affects inhibition of nuclear factors (nuclear factor-κB; NF-κB). SCFAs affect the differentiation of regulatory T (Treg) cells and the production of interleukin-10 (IL-10) with the participation of GPR43. SCFAs also regulate dendritic cell (DC) function. In addition, SCFAs influence AIM2 and NLRP3 inflammasomes activation which then affects production of interleukin-18 (IL-18) and enhanced epithelial barrier function. Moreover, NLRP6 inflammasome activation and secretion of IL-18 regulate the production of intestinal antimicrobial peptides (AMPs) [31][32]. Abbreviations: FOXP3-forkhead box P3; TGF-β-transforming growth factor β.

SCFAs are speculated to have a mediational role in the microbiota–gut–brain axis crosstalk [33]. Two major SCFAs signaling mechanisms have been identified, namely inhibition of HDACs and activation of GPCRs—The binding partners of GPR41 and GPR43 (Table 3) [34][35].

Table 3. The characteristics of SCFAs and lactic acid receptors [8][36][37][38].

Receptor	Ligand	Protein G	Exspression	Physiological Function
FFAR2—Free fatty acid receptor 2 (GPR43)	Acetate, propionate, butyrate	Gi/o, Gq11	Small intestinal epithelium, colonic, colonic LP cells, leukocytes in small intestinal LP, adipocytes, polymorphonuclear cells, skeltal muscle, spleen and heart etc.	Apetite control, anti-lipolysis, increased insulin sensitivity, preadipocyte differentiation, expansion and differentiation of Tregs, protection against IBD, apoptosis of human colon cancer cel line etc.
FFAR3—Free fatty acid receptor 3 (GPR41)	Acetate, propionate, butyrate	Gi/o	Small intestinal epithelium, colonic, colonic LP cells (mast cells), peripheral nervous system, peripheral mononuclear cells, bone marrow spleen, adipocytes, lymph nodes, etc.	Leptin expression, oxygen consumption rate, increased energy expenditure, decreased food intake, hematopoiesis of DCs from bone marrow, increased DC precursors alleviating asthma and Treg cells etc.
HCA1—Hydroxycarboxylic acid receptor 1 (GPR81)	lactate	(Gi)	Predominantly in adipose tissue, minor in kidney, skeletal muscle, liver, intestinal tissue, rat and human brain, mouse primary cortical neuronal cells, macrophages, etc.	Modulation of cortical neuron activity, and enterocyte turnover in response to starvation-refeeding, anti-lipolysis, anti-inflammatory on macrophages, reduced symptom of cancer and IBD in mouse models of hepatitis and pancreatitis, etc.

HCA2—Hydroxycarboxylic acid receptor 2 (GPR109A)	Niacin, ketone bodies, β-hydroxybutyric acids, butyrate	Gi/o, Gβγ	Apical membrane of colonic and small intestinal epithelium, monocytes, adipocytes, macrophages, DCs, neutrophils, retinal pigment epithelium, etc.	Improved epithelial barrier function, anti-lipolysis, decrease of triglyceride, protection against CRC and colitis, increase of Treg generation and IL-10 producing T cells, etc.
Olfr78 (murine) OR51E2 (human)	Acetate, propionate	NR	Neurons, epithelial enteroendocrine cells of colon, enteroendocrine cells, renal afferent arteriole, smooth muscle cells, etc.	Regulation of hormone secretion (GLP-1, PYY) and blood pressure, etc.
PPARγ (Peroxisome proliferator-activated receptor gamma)	Propionate, butyrate	NR	Large intestine adenocarcinoma cells, etc.	Regulation of lipid metabolism, a joining factor between the gut microflora composition and accumulation of the adipose tissue, etc.

Abbreviations: CRC—colorectal cancer; DC—dendritic cell; GLP-1, glucagon-like peptide; GPR—G-protein coupled receptor; IBD—inflammatory bowel disease; IL-10 (interleukin-10); LP—lamina propria; NR—not reported; Olfr—olfactory receptor; PYY—peptide YY; Treg—regulatory T cell.

SCFAs play a very important role in regulating pH, increasing the absorption of calcium, iron, as well as magnesium, and are beneficial for glucose and protein metabolism in the liver. In addition, these acids affect the maintenance of the normal structure, integrity and function of the intestines [19]. They show anti-inflammatory activity, which involves inhibiting the activity of inflammatory mediators in the intestinal epithelium, and thus inhibiting the activation of NFκB macrophages, which are the main source of cytokines in the course of the inflammatory process of inflammatory bowel diseases [19]. These acids are the primary source of energy for colonocytes [39][40]. It has been shown that the source of 70% of the energy used by intestinal epithelial cells (IEC) is butyric acid produced by commensal bacteria, especially such as *Ruminococcus* and *Faecalibacterium* (Table 4) [12]. In addition, by simulating the growth of saprophytic microflora, SCFAs inhibit the development of pathogenic microorganisms such as *Escherichia coli*, *Salmonella,* or *Campylobacter*, competing for colonization sites [6]. Studies have shown that butyric acid stimulates the expression of the MUC2 gene in cell lines and the production of mucin, and the sticky layer it creates protects the intestinal epithelium from contact with toxins and pathogenic microorganisms [41]. In contrast, studies of programmed cell death from a tumor line have demonstrated the effectiveness of butyric acid in inhibiting their development and inducing the process of apoptosis [42][43][44]. In addition, butyric acid and propionic, acetic, and valeric acids have been shown to induce apoptosis (Table 4) [45].

SCFAs increase the amount of mucus produced and the speed of blood flow. More importantly, they provide acetyl-CoA used in the process of fat biosynthesis and cell membrane production, guaranteeing

the integrity of mucous membranes [46]. There are indications that SCFAs are key mediators of the beneficial effects of intestinal microbiota. SCFAs also directly modulate host health through a number of tissue-specific mechanisms associated with intestinal barrier function, glucose homeostasis, immunomodulation, appetite regulation, obesity, and have a direct and indirect effect on cardiovascular disease (CVD) risk markers [47].

At present, relatively little is known about the function of formic acid in the intestines. There are indications that its presence is associated with methanogenesis and its concentration may be elevated during inflammation (Table 4) [48][49]. Acetic acid concentration in the colon is the highest of all SCFAs, and in cells it is a key factor in the metabolism of carbohydrates and fats [50]. In addition, acetic acid is absorbed by the liver, where it participates in the synthesis of cholesterol (Table 4) [51]. Propionic acid is produced in the human gut mainly by *Bacteroidetes* and *Firmicutes* [52]. This acid is an inhibitor of gluconeogenesis and cholesterol synthesis in the liver [53]. In addition, it has antibacterial and anti-inflammatory effects, taking part in the protection of human intestines against pathogens [6][54]. Butyric acid exerts the strongest anti-inflammatory effect of all SCFAs [19]. The cause of the inflammatory process of the intestinal mucosa, which accompanies many pathological processes, is a lack of energy. Butyric acid is the main source of energy for intestinal epithelial cells. Butyric acid has a beneficial immunoregulatory effect on intestinal epithelial cells and other mucosal cell populations. It modulates gene expression by affecting both stimulants and inhibitors of expression. Some of these mechanisms are based on histone hyperacetylation due to inhibition of the histone deacetylase enzyme activity (Table 4) [55].

Unlike other SCFAs, the role of valeric acid in gut health is not fully understood. In a limited number of studies, it was found that valeric acid can stimulate the growth of intestinal epithelium and have a beneficial effect on the pathogenesis of diseases such as colitis, cardio-metabolic diseases and cancer (Table 4) [56][57][58].

Table 4. Examples of trials regarding the effect of SCFAs on human health.

Type of SCFA	The Effect on Human Health	References
Acetate	· Protection against *E. coli* O157:H7 infection	[59]
	· Participates in the synthesis of cholesterol	[51]
	· Is the source of 70% of the energy used by intestinal epithelial cells	[12]
	· Increases in MUC2 gene expression and the production of mucin	[41]
	· inhibits development of tumor cells and inducing the process of their apoptosis	[60][43][44]
Butyrate	· Inhibits the genotoxic activity of nitrosamides and hydrogen peroxide	[61]
	· Has immunoregulatory effect	[55]

	· Plays a role in the prevention and the treatment of distal ulcerative colitis, Crohn's disease and cancer	[62]
	· Improves ulcerative colitis (UC) symptoms	[63]
Butyrate/acetate/propionate	· Improves the macroscopic and histological signs of inflammation	[64]
Formate	· Presence is associated with methanogenesis and its concentration may be elevated during inflammation	[48][49]
Propionate	· Decreases cholesterol synthesis in the liver, improves lipid metabolism	[53][65]
	· Has anti-proliferative effect	[66][67]
Valerate	· Stimulates the growth of intestinal epithelium · Has a beneficial effect on the pathogenesis of diseases such as colitis, cardio-metabolic diseases and cancer	[56][57][58]

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Keywords

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