

Review

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Review

Short-Chain Fatty Acids and Human Health: From Metabolic Pathways to Current Therapeutic Implication

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Abstract: The gastrointestinal tract is colonized by trillions of different microorganisms, named the gut microbiota, which is key to degrade undigested food such as dietary fibers. The fermentation of these food components leads to the production of short-chain fatty acids (SCFA) acetate, propionate, and butyrate, which exploit several beneficial roles for the host's health. Their production and absorption happen in different ways in the human intestine and depend on the type of dietary fiber reaching the gut and the microorganisms involved in the fermentation. The supplementation of SCFAs, mostly butyrate, in treating gastrointestinal, metabolic, cardiovascular, and gut-brain-related diseases has been reported in the medical literature. This review aims to give an overview of the production and absorption dynamics of acetate, propionate, and butyrate in the human gut, with a final focus on the role played by these SCFAs on gastrointestinal and metabolic health and the present therapeutic implications.

Keywords: intestinal microbiota; short-chain fatty acids (SCFAs); dietary fiber fermentation; gastrointestinal and metabolic health; therapeutic implication

1. Introduction

The human gastrointestinal tract is heavily colonized by trillions of microbes that include hundreds of species endowed with a wide range of hydrolases involved in the fermentation of indigestible carbohydrates [1]. Microbial fermentation of polysaccharides is highest in the colon, reaching a daily production rate of 300 mmol/day, of which only 10 mmol/day are excreted [2]. The main volatile short-chain fatty acids (SCFA) produced are acetate, propionate, and butyrate in a ratio of 60:25:15 [3]. Butyrate acts as a key SCFA in the intestine. It serves as the primary energy for the metabolism of colonocytes, improving the integrity of the epithelial tissue, alleviating mucosal inflammation, and stimulating the absorption of electrolytes [4]. Furthermore, dissociated butyric acid can freely penetrate the cytoplasm, inhibiting DNA replication and dissociating the nutrient transport system from bacteria, leading to a broad-spectrum antibacterial effect [5]. Propionate is thought to benefit the gut environment, such as lowering lipogenesis, cholesterol levels and carcinogenesis [6]. Finally, studies demonstrate that acetate can beneficially affect host energy and substrate metabolism in the gut by stimulating the secretion of gut hormones such as the glucagon-like peptide-1 and peptide YY [7]. Thanks to their beneficial properties, SCFA is often used as a supplement to treat different diseases. However, the pharmaceutical formulation of short-chain fatty acid supplements fundamentally impacts their delivery and absorption. After looking at the production of SCFA acetate, propionate, and butyrate in the intestinal environment in the first part of this review, the second part will focus on the absorption of these SCFA. It will give an overview of

SCFA supplements used in clinical trials, with particular attention to their formulations. Moreover, the importance of SCFAs in gastrointestinal and metabolic health will be discussed, concluding with the existing therapeutic implications.

2. Production of SCFA in the Gastrointestinal Tract

2.1. Cross-Feeding and Production of SCFA in the Human Intestine

Microbial communities are shaped by positive and negative interactions ranging from competition to mutualism. Millions of microbial inhabitants are present in the mammalian gut, and the interactions between these microbes produce synergistic responses [8]. Many ecological dynamics are mediated by diffusible metabolites, which can act as nutrient sources, inhibitory compounds, or signaling molecules [8]. Cross-feeding is the exchange of metabolites as energy and nutrients among different specimens or strains of microorganisms [9]. Other types of cross-feeding within the gut microbiome exist parasitism, commensalism, and mutualism. Parasitism occurs when one microbe benefits from a substrate produced by a partner organism while changing the environment to harm this producer. On the other hand, mutualism cross-feeding results when one consumer feeds on metabolites produced by another microbe with no impact on the latter. Finally, commensalism cross-feeding occurs when two species feed on a metabolite produced by the other or when one microbe feeds on a metabolite from another and modifies the environment to benefit the producer. It is essential to mention that for many species, cross-feeding fermentative intermediates is an integral part of their lifestyle in the gut. Important fermentative intermediates are SCFAs and carboxylic acids with a short aliphatic tail of 6 carbons, especially acetate (C2), propionate (C3), and butyrate (C4). Some species of bacteria produce These metabolites under anaerobic conditions upon fermentation of dietary fibers, mainly oligofructose, arabinoxylan, inulin, and pectin [10]. However, other factors, such as the low pH (5.5), are likely to beneficially affect the colon's community structure and microbial activities [11,12]. This consideration may be necessary, for example, to allow butyrate-producing bacteria to compete against carbohydrate-utilizing bacteria, such as *Bacteroides* spp., which, on the other hand, prefer a pH of 6.5 [13].

2.2. Production of Acetate by the Intestinal Microbiota

Acetate is a net fermentation product for most gut anaerobes and almost invariably achieves the highest concentration among SCFAs in the gut lumen [14]. Microbial-derived acetate production is yielded by the fermentation of indigestible foods, especially foods of acetogenic fibers such as galacto-oligosaccharides (GOS) and inulin [15]. Microbial fermentation of acetogenic fibers generates acetate production via two metabolic pathways: acetogenesis and carbon fixation. The former consists in the production of acetate, mediated by homoacetogenic bacteria or acetogens, which are able to produce acetate from H_2 and CO_2 ; while the carbon fixation pathway produces acetate from CO_2 as a precursor, and it is also known as the WOOD-Ljungdahl pathway [16]. In particular, this trend is accompanied by an increase of the *Firmicutes/Bacteroidetes* ratio and cross-feeding mechanisms, as reported by the upregulation of pyruvate fermentation pathways to acetate and lactate by *Lactobacillus reuteri* and other unclassified bacteria [17]. Other studies support these findings, describing increased abundance of important acetate producers, such as *Akkermansia muciniphila*, during human fasting and caloric restriction interventions [18,19]. This intermediate is of particular interest because it can be further metabolized by acetate-consumers, such as *Faecalibacterium prausnitzii* and *Roseburia intestinalis/Eubacterium rectale* to produce butyrate [20]. More specifically, it has been reported that acetate is a growth requirement for these bacteria [20,21]. Thus, it is an essential intermediate in the intestine.

2.3. Production of Propionate by the Intestinal Microbiota

Propionate is a SCFA that can derive mainly from two essential pathways through the fermentation of different carbohydrates by gut bacteria: i) the succinate pathway consists of the fermentation of hexose and pentose sugars with the production of propionate, while ii) the propanediol pathway produces propionate through fermentation of fructose and rhamnose. The former is found mainly in *Bacteroidetes* and in the *Negativicutes* class of *Firmicutes* [21], and it is the primary route for propionate formation from dietary carbohydrates fermentation as the abundant

Bacteroidetes drive it. In particular, succinate is a precursor of propionate, and its conversion to propionate requires vitamin B12 [22]. Propionate formation from rhamnose and fructose has been reported in gut bacteria belonging to the Lachnospiraceae family, including *Roseburia inulinivorans* and *Blautia* species [21]. Besides carbohydrates, peptides and amino acids can also be precursors for propionate formation. However, amino acid-fermenting bacteria have been estimated to constitute less than 1% of the large intestinal microbiota. In particular, Bacteroidetes are responsible for propionate formation by proteolysis from peptides and amino acids [23]. More specifically, *in vitro*, incubations of fecal slurries with individual amino acids reported that propionate derived mainly from aspartate, alanine, threonine, and methionine [24]. Finally, cross-feeding between different commensal gut bacteria is also essential in propionate production. Indeed, bacteria belonging to *Bacteroides* species, *Escherichia coli*, and *Anaerostipes rhamnosivorans* can degrade deoxy sugars by producing the pathway intermediate 1,2 propanediol as the final product. *E. hali* and *Lactobacillus reuteri* can further degrade this intermediate with propionate formation [25]. Although propionate is less frequently studied compared to other microbial metabolites, such as butyrate, it has been reported that it also has some distinct health-promoting properties, including cholesterol-lowering [26] and antilipogenic [27] effects, stimulation of satiety [28] and protection against colorectal cancer in particular [29]. Its beneficial effect in the contest of gastrointestinal diseases, particularly inflammatory bowel diseases (IBD) and inflammatory bowel syndrome (IBS), will be discussed in more detail in the third part of this review.

2.4. Production of Butyrate by the Intestinal Microbiota

Production of butyrate can derive from different pathways: butyrate formation by synthesis from acetoacetyl-CoA, which is formed by the reaction of two molecules acetyl-CoA: Butyryl-CoA, acetate CoA-transferase converts butyryl-CoA to generate butyrate. This has been observed in *Eubacterium*, *Roseburia*, *Anaerostipes* and *Faecalibacterium prausnitzii* [3]. Another route of butyrate formation is through the phosphotransbutylase and butyrate kinase. For example, specific *Coprococcus* species and numerous *Clostridium* species in the Firmicutes family have butyrate kinase to generate butyrate [30]. Among Firmicutes, the two most abundant gut bacteria families of butyrate producers are *Ruminococcaceae* and *Lachnospiraceae*. *Faecalibacterium prausnitzii* belongs to the family of *Ruminococcaceae* and is one of the most abundant species in the healthy human microbiota [23]. As previously mentioned, this bacteria produces butyrate via butyryl-CoA: acetate CoA transferase with net consumption of acetate, which stimulates its growth on carbohydrate energy sources [20]. In particular, this bacterium has gained increasing interest in recent years thanks to evidence reporting its anti-inflammatory properties in the intestine. Due to its beneficial properties, it has attracted interest as a potential therapeutic for patients suffering from IBD, whose microbiota usually are deprived of this bacteria [31].

Butyrate-producing Lachnospiraceae show considerable divergence in their phylogeny, gene organization, and physiology [32]. *Eubacterium rectale* and *Roseburia* species are closely related and constitute a significant group of butyrate-producing Firmicutes through the butyryl-CoA: acetate CoA transferase route. It is of interest to note that in some *Roseburia* strains, at mildly acidic pH, butyrate is almost the sole fermentation acid produced, with net consumption of acetate accompanying the formation of butyrate. On the other hand, other strains also produce formate and lactate in addition to butyrate [32]. Moreover, certain Lachnospiraceae, including *A. hardus* and *E. hali*, have the ability to grow in the presence of lactate and produce butyrate [33]

Also, butyrate can be formed through the fermentation of peptides and amino acids. An example is *Intestinimonas* AF211, which ferments lysine to butyrate [34]. Moreover, several distinct pathways exist for glutamate degradation to butyrate in butyrate-producing bacteria. These intermediates enter the main butyrate pathway either via pyruvate (*Fusobacterium* spp, *Clostridium limosum*) or crotonyl-CoA (found in different Firmicutes, including *Acidaminococcus symbiosum*, *Clostridium sporosphaeroides*, *Clostridium symbiosum*, etc). As it concerns the fermentation routes of other amino acids, these are less well characterized [35]. However, there is evidence that histidine is converted to glutamate, which is further fermented to butyrate by the intestinal microbiota [36,37]. An overview of the production of the three different SCFA and the metabolic pathways and bacteria involved is represented in Table 1.

Table 1. Production of the three different SCFA forms different pathways and by other intestinal bacteria.

SCFA	Metabolic pathway	Bacteria involved in the production
acetate	Acetogenesis	<i>Acetobacterium</i> , <i>Acetoanaerobium</i> , <i>Acetogenium</i> , <i>Butyrbacterium</i> , <i>Clostridium</i> , <i>Eubacterium</i> , <i>Pelobacter</i> <i>Bacteroides succinogenes</i> , <i>Clostridium</i> <i>butyricum</i> , <i>Syntrophomonas</i> sp.
		Firmicutes (<i>Bacteroidetes</i> and <i>Negativicutes</i>)
		Lachnospiraceae (<i>Roseburia</i> <i>inlinivorans</i> , <i>Balutia</i> sp.)
Propionate	Carbon fixation	
Butyrate	Butyryl-CoA : acetate-CoA transferase	<i>Eubacterium</i> , <i>Roseburia</i> , <i>Anaerostipes</i> , <i>Faecalibacterium</i> <i>prausnitzii</i>
	Butyrate kinase	specific <i>Coprococcus</i> species and <i>Clostridium</i> species

2.5. Cross-Feeding Lays the Basis of Butyrate Production by Intestinal Microbiota

As previously mentioned, the production of SCFAs and other intermediates depends on the dietary fibers and, in lower amounts, on peptides and amino acids metabolized by the intestinal bacteria. These food components belong to the prebiotics category: non-digestible food ingredients that beneficially affect the consumer by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon [38]. Examples of industrial prebiotics are, for example, inulin-type fructans, GOS, and fructooligosaccharides (FOS) [39]. Inulin-type fructans are naturally present in different vegetables, such as onions, garlic, leek, bananas, and chicory roots. These compounds encompass short and long polymers of fructose with varying degrees of polymerization. Because of their β -linkages, inulin-type fructans are not digested nor absorbed in the human gastrointestinal tract [40]. Once these fibers reach the colon, they are selectively fermented by the microbiota, mainly by the bifidobacterial communities. During the complex colon fermentation process, they are primarily converted to SCFAs and other organic acids (e.g., lactate and succinate) and gases (hydrogen gas and carbon dioxide) [41]. In particular, the presence of unfermented inulin-type fructans in the intestine elicits the growth of intestinal Bifidobacteria, the so-called bifidogenic effect [42], as well as an enhancement of colonic butyrate production, the so-called butyrogenic effect [42], promoted by Bifidobacteria, and thanks to the cross-feeding phenomenon [11]. In the case of inulin-type fructans, two main types of cross-feeding have been reported: one involving short oligosaccharides and monosaccharides released by *Bifidobacterium* from the prebiotic substrate; the other one using consumption of end-products of bifidobacterial fructans fermentation, including acetate and lactate [43]. For example, *E. hali* DSM 17630 has been shown to efficiently convert lactate and acetate produced by *B. adolescentis* DSM 20083 into butyrate, when growing in co-culture with oligofructose [43]; moreover *A. caccae* DSM 14662 in co-culture with *B. longum* BB536 convert acetate and fructose produced by the latter strain during substrate breakdown [44]. Although clostridiales species form a minor fraction of the human colon microbiota (5-10%), butyrate formation by strict anaerobic bacteria, including *Clostridium* genus has been known for a while. In particular, more than 90% of the colonic butyrate-producing bacteria are represented by *Faecalibacterium prausnitzii* (*Clostridium leptum* cluster) and *Eubacterium/Roseburia* spp (*Clostridium coccoides* cluster). The rate of butyrate formation by acetate-consumers (e.g., *F. prausnitzii* and *Roseburia intestinalis*) can vary depending on the species of butyrate-producing bacterium and the type of fermentable carbohydrate

[8]. Indeed, besides inulin-type fructans, the butyrogenic effect is already known in the case of resistant starch fermentation [45], and *in vitro* studies have reported an efficient butyrate production in a co-culture of *B.longum* JCM 1217 and *Eubacterium limosum* JCM 6421 on germinated barley. In this case, the former strain produces lactate upon starch degradation, while the latter uses lactate for butyrate production [46]. Another study recently reported an efficient cross-feeding between *R. intestinalis* (a butyrate producer) and *Ruminococcus hydrogenotrophicus* (an acetate producer) when growing on xylan. In this context, xylan degradation first occurs thanks to *R. intestinalis*, which produces carbon dioxide and hydrogen gas, which serve as substrates for *R. hydrogenotrophicus* to grow, along with the production of acetate. This SCFA is then an indispensable co-substrate for butyrate production [47]. An overview of the production of SCFAs in the gut by the microbiota is represented in Figure 1.

As previously mentioned, researchers have lately been drawn to the study of butyrate because of its beneficial properties in the intestinal environment. Indeed, butyrate has been reported to have essential effects on intestinal cell development and gene expression [4,48] and is generally thought to play a protective role against colorectal cancer and colitis. Its beneficial roles in the context of gastrointestinal and metabolic diseases will be discussed in more detail in the third part of this review.

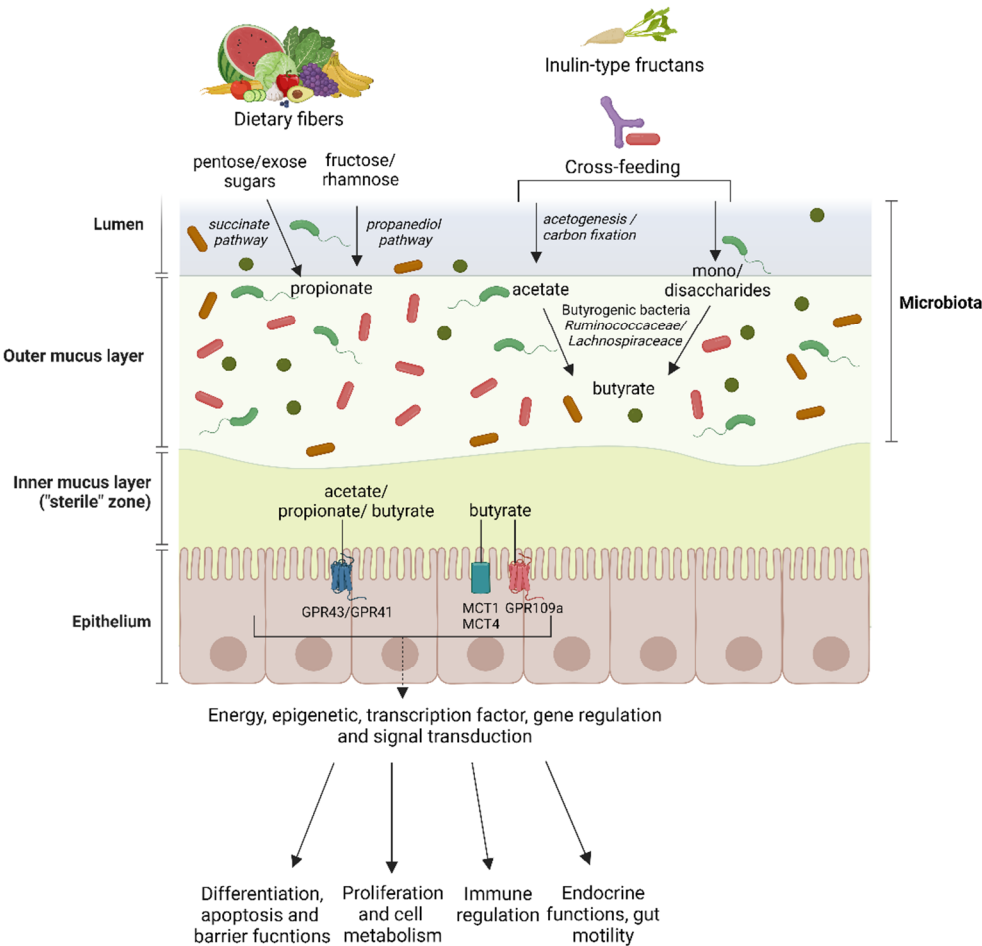


Figure 1. Production and absorption of SCFAs acetate, propionate, and butyrate in the human intestine. Effect on gastrointestinal and metabolic health.

3. Absorption of SCFAs in the Intestine and SCFA Supplements

3.1. Absorption of Butyrate

For many years, it was believed that the primary mechanism of butyrate absorption was passive diffusion in its liposoluble form [48]. Today, considerable evidence suggests that SCFAs, including butyrate, are predominantly absorbed through a facilitated process involving a series of transport proteins. The characterization of several transmembrane proteins has led to the identification of two well-defined absorption pathways, both involving monocarboxylate transporters: MCT1 and MCT4 [49,50], two hydrogen-coupled transporters, and SMCT1, a sodium-coupled transporter [51].

From the early studies conducted by Thibault et al., assessing butyrate absorption in diseased colon tissue from Inflammatory Bowel disease (IBD), Familial Adenomatous Polyposis (FAP), and colorectal cancer (CRC), it was highlighted that MCT1 mRNA was drastically reduced in diseased tissues and correlated with the degree of inflammation. Functionally, this was demonstrated by a reduction in butyrate absorption and metabolism [52]. In cancerous tissue (CRC), however, there are peculiarities: while MCT1 expression decreases during the transition from normal to malignancy, being downregulated in the early stages of carcinogenesis [53], a subsequent upregulation of MCT1 has been described in advanced metastatic CRC tumors. In these tumors, MCT1 and MCT4 transporters play a crucial role in lactate transport and, consequently, intracellular pH regulation. Inhibiting MCT1 reduces intracellular pH, leading to tumor cell death. In this context, MCT1 and MCT4 can be potential therapeutic targets in cancer treatment [54–56]. Butyrate has been previously approved for clinical use in CRC treatment [57], as it is a substrate for MCT1 and MCT4, is well metabolized, and no side effects have been reported until now [58]. In contrast to the MCT1 receptor, knowledge regarding the regulation of SMCT1 at the intestinal level is still limited. SMCT1 is downregulated during intestinal inflammation, and its expression is often silenced in aberrant crypt foci, colon adenomas, colon tumors, and colon cancer cell lines, suggesting that SMCT1 silencing is an early event in colon tumorigenesis [59–62]. It has been proposed that SMCT1 functions as a tumor suppressor, and its ability to mediate butyrate entry into colonocytes underlies its potential tumor-suppressive function [63].

Also noteworthy among the control and interaction systems with butyrate are the so-called efflux transporters, capable of removing butyrate from cells. Among these, Breast Cancer Resistance Protein (BCRP) is believed to limit drug absorption, bioavailability, and toxicity. Butyrate is a substrate for BCRP [64], and the inhibition of BCRP has significantly potentiated the inhibitory effect of butyrate on cell proliferation [65]. After absorption, butyrate signals through three membrane G-protein-coupled receptors (GPCRs), GPR41, GPR43, and GPR109A, present on the surface of colon cells, adipocytes, and immune cells. These receptors modulate cytokine levels and various signaling pathways when activated, promoting the anti-inflammatory response [66].

3.1.1. Butyrate Supplements

The literature generally presents studies conducted using two different formulations of butyrate: calcium butyrate (CaBu) and sodium butyrate (NaBu). Sodium butyrate and calcium butyrate are salts of butyric acid but differ in the metal to which they are bound. Calcium and sodium are the primary cations in the extracellular space, with calcium exhibiting reduced water solubility compared to sodium [67]. The choice of butyrate formulation with associated metal could be significant in treating patients with specific conditions or deficiencies [68]. The formulation of CaBu associated with vitamin D may be particularly interesting, especially for cancer prevention [69]. NaBu formulations, depending on the inflammatory context, may contribute to protective immunity relative to the associated ion [68]. It has been demonstrated that sodium storage in tissues improves defense against invasive pathogens [70]. However, immune activation induced by sodium salt may also negatively influence wound healing [71]. It should be noted that the concentration of salts coupled with butyrate is generally in the order of a few milligrams, depending on the formulation examined.

Table 2. Effects of butyrate interventions in IBD and **non-IBD conditions**. Abbreviations: s= significant improvement, nr= Information not reported, std = Standard therapy, ns=Not significant improvement, ps=Partial significant effect DC=Diverting Colitis, DB=Double Blind, SB=Single Blind; UC=Ulcerative Colitis; CD= Crohn disease, A-S= Mesalamine+Sulfasalazine, CRP=Cronic Radiation Proctitis, ARP=Acute Radiation Proctitis, DM=Diabetes mellitus, DT1=Type 1 diabetes, DT2=Type 2

diabetes , Ob ped=Obese pediatrics, COPD=Chronic obstructive pulmonary disease, not impr.= not improvement.

Ref.	Delivery	Year	Groups(n)		Design	Duration	Dosage	Butyrate	Drugs(ad)	Improveme nt
[72]	enema	1991	DC (13)		DB	2w	40mmol/Lit		nr	ns
[73]	enema	1992	UC (10)		SB crossover	2w	100mmol/Lit		A-S	s
[74]	enema	1994	UC (10)		open label	6w	80mmol/Lit		A-S	60%
[75]	enema	1995	UC (40)		DB-RCT	6w	200ml/d mix		A-S	s
[76]	enema	1996	UC (38)		RCT	6w	80mmol/d		A/S	not improve.
[77]	enema	1996	UC (47)		DB-RCT	6w	80mmol/d		nr	not impr.
[78]	enema	1999	CRP (17)		DB-RCT	5w	80mmol/d		nr	s
[79]	enema	2000	UC (30)		RCT	6w	4gr/d		A	ns
[80]	enema	2000	APR (20)		RCT crossover	3w	80mmol/Lit		nr	s
[81]	enema	2002	UC (11)		RCT	8w	100mM		A/S/steroid	s
[82]	enema	2003	UC (51)		DB-RCT	6w	80mmol/Lit		M/steroid	S
[83]	oral	2005	CD (13)		open label	8w	4gr/d		A/S	69%
[84]	oral	2008	UC (216)		open label	24w	921mg/d		A+S	82,4%
[85]	enema	2009	IBS (11)		DB-RCT	1w	50/100mmol/Lit/dnr			s
[86]	enema	2010	UC (35)		DB-RCT crossover	20d	100mmol/d		nr	s
[87]	oral	2013	IBS (66)		RCT	12w	300mg/d		std ⁹	s
[88]	oral	2014	DC (63)		RCT	12month	300mg/d		nr	s
[89]	oral	2014	TD (42)		RCT	3d+trip	1500mg/d		various	s
[90]	enema	2014	APR (166)		RCT	3w	1-2-4gr/d		nr	ns
[91]	enema	2016	Mix (20)		DB-RCT	4w	600mmol/Lit		nr	s
[92]	oral	2017	DM (40)		DB-RCT	45d	600mg/d		+inulin	s(+ inulin)
[93]	oral	2020	UC (39)		Prospective	12months	1g/d		std	s
[94]	oral	2020	IBD (49)		DB-RCT	8w	600mg/d		std	ps
[95]	oral	2020	DT1 (30)		DB-RCT	4w	4g/d		nr	no
[96]	oral	2022	Ob ped (54)		QB-RCT	13 months	20mg/kg		std	s
[97]	oral	2022	IBD (80)	ped	RCT	12w	150mg/d		std	no
[98]	oral	2022	DT2 (42)		TB-RCT	6w	600mg/d		nr	s
[99]	oral	2024	COPD (121)		RCT	12w	300mg/d		nr	s

In addition to the formulation, the type of pharmaceutical form used for product delivery should also be carefully evaluated based on the site of action and the desired effect. Although several studies have reported beneficial effects of butyrate in the colon [100], some *in vitro* studies [101] and others conducted on mice have shown that butyrate enemas administered for three consecutive days induced concentration-dependent colon hypersensitivity (from 3-8 up to 1000 mmol/L) and mechanical hyperalgesia but no macroscopic and histological modification of the colon mucosa. This condition mimics the clinical condition observed in patients with IBS and is used as a model of chronic non-inflammatory colon hypersensitivity [102]. However, in human subjects, a comparable administration of butyrate in the distal colon decreases pain and discomfort, sharply contrasting with studies in rats. Some scholars attribute this difference to the different modulation of butyrate-coupled receptors in rats and humans and the concentration of butyrate present in the colon after exogenous administration compared to that naturally present given endogenous butyrate production [103]. It is reasonable to think that the pharmaceutical formulation may be functional in the butyrate concentration in the colon and have a pharmacological effect on the examined pathology [94]. Oral formulations with gastro-resistant capsules, microencapsulation, or enemas (see Table 2) may have different effects in different parts of the body, as the concentration of butyrate reaching the tissues may vary depending on the pharmaceutical form's ability to release the product [104]. Lipid microencapsulation rather than protection in gastro-resistant capsules allows n-butyric acid compounds to first not diffuse the unpleasant odor of rancid butter that characterizes the product and secondly not be readily hydrolyzed by gastric acids and thus reach the small intestine and colon where they can exert their function. New cream formulations based solely on butyrate [105] and free of corticosteroids are currently on the market and could prove helpful in controlling local inflammations, preventing the side effects associated with corticosteroids [106]; however, to date, there are no clinical studies evaluating their effectiveness.

3.2. Absorption of Propionate

Propionate has been associated with reducing lipogenesis and serum cholesterol levels [107]. It elicits strong effects on weight control and eating behavior [108]. It has also been demonstrated that, like butyrate, propionate exerts an antiproliferative effect on colon tumor cells [109,110]. The production of propionate by intestinal bacteria involves the transformation of prebiotic compounds such as L-rhamnose, D-tagatose, inulin, resistant starch, polydextrose, and arabinoxylans [6]. However, it isn't easy to perform a comparative assessment of the modulatory effects of propionate of such compounds due to the heterogeneity of the experimental setup of the studies. It should be emphasized that a direct connection between the production of SCFAs and their concentration in the intestinal lumen can only be established in an *in vitro* context without intestinal absorption.

The mechanisms of propionate production involve specific fermenting bacteria that use specific metabolic strategies, as previously mentioned. The propionate thus produced is easily transported systemically [111,112], passing through the liver. In general, propionate and acetate can activate GPR41 and GPR43 cell surface receptors but can also be easily absorbed at the level of any cell, bypassing SCFA receptors on the cellular surface. It has been shown that propionate also enhances the differentiation of T cells into effector cells such as Th1 and Th17 in favor of regulatory T cells producing anti-inflammatory IL-10 [113]. This regulation is essential for maintaining intestinal homeostasis and preventing chronic IBD.

3.2.1. Propionate Supplements

Unlike butyrate, formulations of propionate used for supplementation have been rarely studied in clinical trials (especially in obesity, diabetes, and cardiovascular disease, see Table 3). Recently, supplementation of propionic acid administered twice daily with 500 mg capsules for a 14-day treatment period in patients with multiple sclerosis (MS) has shown a significant increase (30%) compared to baseline in Treg cells and a reduction in Th17 cells [114], correlated with the attenuation of clinical symptoms (reduction in relapse and stabilization of disability). In a crossover RCT, administering an inulin-propionate ester formulation for 24 weeks to overweight adult subjects confirmed that increased propionate in the colon prevents weight gain in enrolled subjects [115]. Currently, two clinical trials are evaluating the effect of sodium propionate in subjects with various types of pathologies, but none of them in the gastroenterological field (Table 3a). Given the growing

clinical evidence on the immunomodulatory effects of propionate, an increase in well-structured clinical studies is hoped, particularly in the context of chronic intestinal inflammations.

Table 3. Effects of propionate interventions. Abbreviations: s=significant improvement, ACVD=Atherosclerotic cardiovascular disease, HovF=Healthy overweight females, MS= multiple sclerosis IPE= inulin-propionate ester, DB=Double Blind, NaP= sodium-propionate.

Ref.	Delivery	Year	Groups(n)	Design	Duration	Dosage	Propionate Formula	Improvement
[115]	oral	2015	Obese(60)	DB-RCT	24w	10g/d	IPE	s
[116]	oral	2019	Obese(12)	DB-RCT cross over	42d	20g/d	IPE	s
[117]	oral	2019	HovF(20)	RCT	4w	10g/d	IPE	s
[114]	oral	2020	MS(36)/Healthy(68)	proof-of-concept	2w	1g/d	NaP	s
[118]	oral	2022	ACVD(62)	DB-RCT	8w	1g/d	propionic acid	s

Table 3. a. Currently recruiting and upcoming clinical trials examining the effects of propionate.

Name of trial	Type	Identifier /status	condition	intervention	Location
Combination of Medium Cut-off Dialyzer Membrane and Diet Modification to Alleviate Residual Uremic Syndrome of Dialysis Patients	RCT	NCT04247867/ recruiting	Uremic syndrome	Psyllium-inulin/propionate sodium	University medical Centre Ljubljana, Slovenia
The Effect of Combining Medium Cut-Off Dialysis Membrane and Diet Modification on Reducing Inflammation Response	RCT	NCT04247867/ recruiting	Uremic syndrome	Psyllium-inulin/propionate sodium	University medical Centre Ljubljana, Slovenia

3.3. Absorption of Acetate

Although less studied than butyrate, acetate could also be of interest as it is less toxic to epithelial cells, stimulates bacteria that produce butyrate through cross-feeding, and has anti-inflammatory and protective properties [119]. Receptors like GPR43, which play an essential role in calcium homeostasis, are susceptible to acetate and propionate [120]. The probiotic activity of *Saccharomyces cerevisiae* var. *boulardii* is believed to be closely associated with its unusually high production of acetate [121]. The mechanism of action of acetate on intestinal cells is less known, but an interesting aspect is the positive effect that acetate has shown on body weight control. In mice, acetate administration can impact body weight control through effects on energy intake and expenditure [122]. In humans, studies on long-term oral acetate supplementation or endovenous/gastric infusion in the colon with weight loss and energy expenditure as primary outcomes are limited [7], and cross-sectional/cohort analyses have shown inconsistent results with obesity and adiposity [80]. The primary acetate source remains dietary integration through dairy products, pasta, bread, eggs, smoked fish, and coffee [123]. Other significant sources include ethanol, vinegar, and microbial production obtained from fermentation of indigestible carbohydrates (particularly acetogenic fibers like inulin and galactooligosaccharides [15].

3.3.1. Acetate Supplements

The most commonly used formulations in clinical studies are inulin acetate ester and sodium acetate, administered in the proximal colon by enema. As already reported for propionate, clinical studies regarding the use of acetate do not directly involve gastrointestinal disorders but rather the effect of oral supplementation of fermented foods for weight control [122]. Table 4 reports the impact of acetate interventions on hyperinsulinemic females.

Table 4. Effects of acetate interventions. Abbreviations: HinsF= Hyperinsulinemic females.

Ref.	Delivery	Year	Groups(n)	Design	Duration	Dosage Propionate	Formula	Improvement
[124]	Rectally intravenous	and 2010	HinsF(6)	open label	4 times	60mmol/lit rectal+20mmon /Lit intravenous	NaAcetate s	
[125]	Intravenous	2012	Overweight normoglycemic and hyperglycemic subjects (9)	open label	90	140mmol/Lit	NaAcetate	no
[126]	Proximal distal colonic	and 2016	Obese(6)	DB-RCT crossover	3d	100- 180mmol/lit	Acetate	s
[127]	Colonic infusions	2017	Obese(12)	DB-RCT cross over	4d	200mmol/lit mix	(acetate, propionate, and butyrate)	s

4. Implications of SCFAs in Human Gastrointestinal and Metabolic Health

Several studies have indicated the involvement of SCFA in human GI and metabolic health. SCFAs are thought to have pleiotropic effects on gastrointestinal and metabolic health. The identified signaling mechanisms of SCFAs may function through two main mechanisms. The first is via interactions with GPCRs, as previously described, expressed in various organs, including the intestine, kidney, and heart [128–130]. These receptors are expressed in various cell types within the gastrointestinal tract, including enterocytes, enteroendocrine cells, immune cells, and neuronal cells,

mediating a range of physiological responses [130]. The second acts as a histone deacetylase (HDAC) inhibitor [131,132], promoting gene expression and regulating cell metabolism, differentiation, and proliferation by inhibiting specific gene transcription [133–135].

4.1. Gastrointestinal Diseases

SCFAs play a critical role in maintaining gut health and have been implicated in various gastrointestinal diseases, including IBD, CRC, and disorders of the gut-brain axis. The supposed mechanisms of SCFA are summarized in Table 5.

Table 5. Mechanisms of SCFA in gastrointestinal diseases.

Disease	Supposed Mechanisms of SCFA Protection/Risk
Inflammatory bowel disease	1. Anti-inflammatory effects: Butyrate, a primary energy source for colonocytes, inhibits NF-κB activation, reducing proinflammatory gene expression. 2. Maintenance of gut barrier integrity: SCFAs promote mucus production and tighten epithelial cell junctions, enhancing the intestinal epithelial barrier. 3. Modulation of immune responses: SCFAs influence the differentiation and function of regulatory T cells (Tregs), suppressing excessive immune reactions. They engage with receptors like GPR43 and GPR109A to stimulate Treg production 4. Tissue repair and healing: SCFAs promote the proliferation and differentiation of epithelial cells, facilitating tissue repair processes within the gut damaged by inflammation in IBD.
Colon cancer	1. Protective effects against CRC development: SCFAs exert protective effects against colorectal cancer (CRC) by regulating gene expression, promoting apoptosis, and inhibiting CRC cell proliferation and metabolism. 2. Anti-inflammatory actions: SCFAs mitigate inflammation in CRC by inhibiting NF-κB activation, decreasing pro-inflammatory cytokine expression, and promoting anti-inflammatory cytokines and regulatory T-cell differentiation. 3. Potential DNA damage modulation: While SCFAs are anticipated to decrease DNA damage in CRC cells, reports suggest they may exacerbate DNA damage accumulation in some instances, possibly due to disruptions in DNA repair mechanisms. Further evidence is needed.

Disorders of the Gut-Brain Axis	1. Neuroprotective effects: SCFAs exert neuroprotective effects by influencing brain function, regulating blood flow, and modulating neuroinflammation via interactions with specific receptors and epigenetic modulation.
	2. Role in neurodegenerative diseases: Reduced SCFA levels are implicated in neurodegenerative diseases like Alzheimer's and Parkinson's. They contribute to intestinal barrier impairment, the release of pro-inflammatory molecules, and microglial activation, ultimately impacting disease progression.
	3. Gut barrier function and motility: SCFAs promote mucus secretion and strengthen intestinal tight junctions, improving barrier integrity. SCFAs can influence nerve activity, neurotransmitters, and muscle contractions.

4.1.1. Inflammatory Bowel Disease

The interaction between SCFAs and IBD is multifaceted, involving the interplay among gut microbiota, immune responses, and the integrity of the gut epithelial barrier [136,137]. Butyrate, a primary energy source for colonocytes, exerts anti-inflammatory effects by inhibiting the activation of the nuclear factor kappa B and reducing proinflammatory gene expression [138]. A decline in SCFA-producing bacteria characterizes IBD patients, notably butyrate producers like *Faecalibacterium prausnitzii* and *Roseburia hominis* [139–141]. This results in reduced colonic SCFA levels linked to compromised gut barrier function in IBD [142,143].

SCFAs protect against IBD-associated intestinal inflammation through various mechanisms [144]. They enhance the intestinal epithelial barrier by promoting mucus production and tightening tight junctions between epithelial cells [144]. Additionally, SCFAs modulate immune responses by influencing the differentiation and function of Tregs, suppressing excessive immune reactions [145]. Several pathways are involved in SCFA-mediated immune regulation, including GPCRs, HDACs, and the regulation of innate immune sensors like Toll-like receptors (TLRs) and Nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome. SCFAs inhibit the progression of IBD by regulating innate immune sensors, TLRs, and NLRP3 inflammasomes. SCFAs protect the intestinal barrier; acetate, propionate, and butyrate stimulate the intestinal NLRP3 inflammasome, increasing IL-18 secretion and enhancing intestinal barrier integrity [146]. Moreover, SCFAs engage with GPR43 and GPR109A receptors essential for regulating intestinal immunity, stimulating the production of Treg. This has been demonstrated in preclinical studies, where controlling colonic Treg levels and function in a GPR43-dependent manner has been shown to mitigate inflammation, as seen in SCFA-mediated protection against colitis in GPR43-deficient (*Gpr43*($-/-$)) mice [147,148]. Furthermore, SCFAs promote the differentiation of Tregs by inhibiting HDAC activity, and Tregs secrete protective cytokines, such as IL10, to suppress inflammation [149]. SCFAs not only inhibit TLR signaling, but butyrate acts as an HDAC inhibitor to suppress TLR4 expression and the TLR2-mediated release of inflammatory factors [150–152]. Finally, SCFAs participate in tissue repair processes within the gut, promoting the proliferation and differentiation of epithelial cells, thus facilitating the healing of damaged tissues caused by inflammation in IBD [153].

A recent study investigated the utility of fecal SCFA concentrations as surrogate markers for gut microbiota diversity in patients with IBD and primary sclerosing cholangitis (PSC) [154]. Results decreased fecal isobutyrate levels compared to healthy controls. Fecal acetate and butyrate positively correlated with fecal calprotectin and serum C-reactive protein in ulcerative colitis (UC) patients. Furthermore, UC patients with higher fecal calprotectin levels exhibited elevated fecal acetate, butyrate, and propionate levels. These findings suggest potential associations between SCFA levels and disease activity in UC patients.

Although SCFA concentrations are decreased in IBD patients, SCFA supplementation through diet or probiotics shows promise as an adjunct therapy, with minimal adverse effects reported [139,153,155–158]. However, the exact mechanisms underlying the therapeutic effects of SCFAs in

IBD require further elucidation, highlighting the complexity of their relationship with the disease. Figure 2 illustrates the mechanism of action of SCFAs.

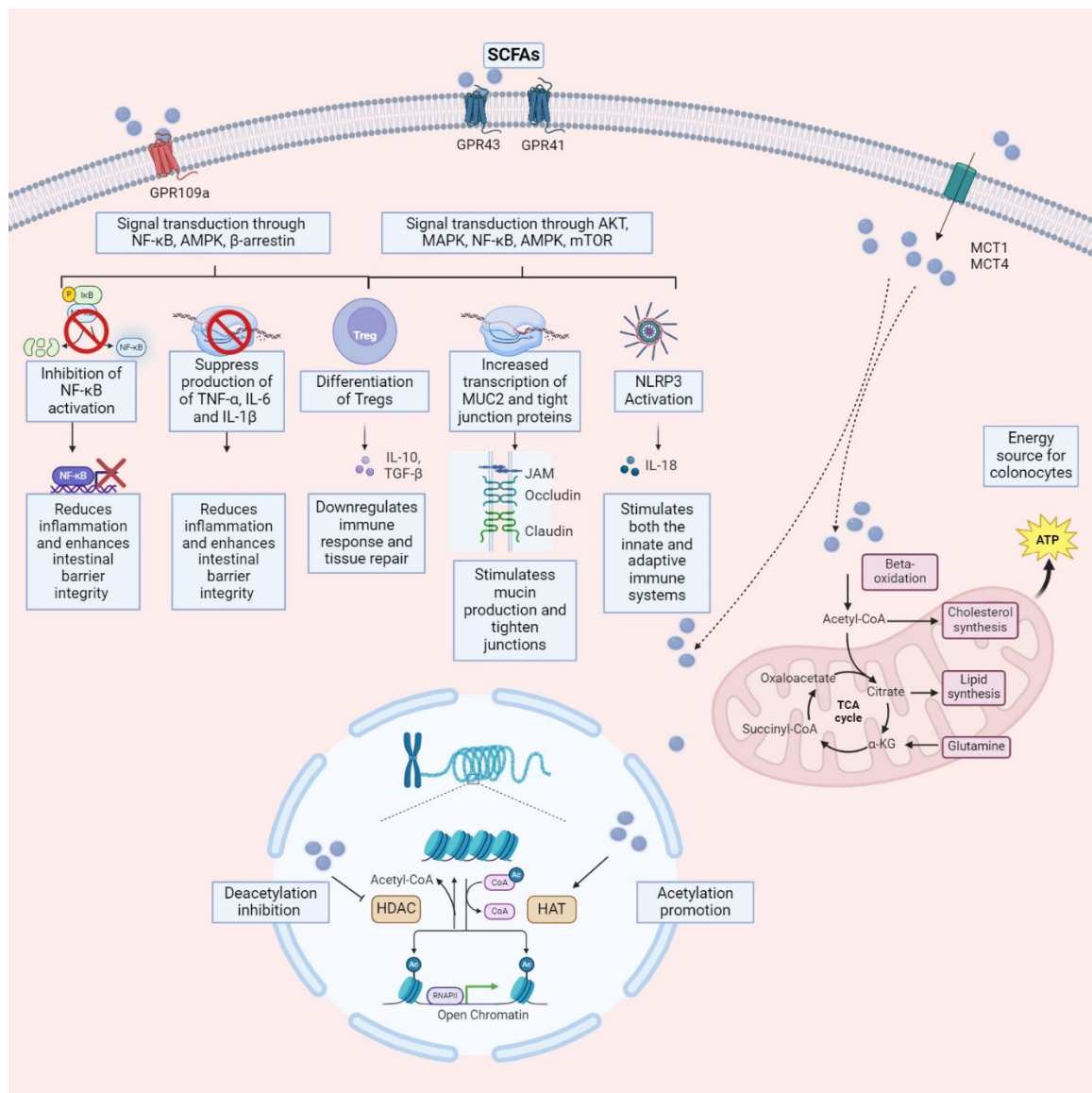


Figure 2. Mechanism by which SCFAs exert their effects on target cells. SCFAs enter cells via MCT and transporters located on the cell membrane. Once inside the cell nucleus, they inhibit HDAC and activate HAT, facilitating histone acetylation. This process gradually relaxes compacted chromosomes, ultimately resulting in increased gene expression. Additionally, upon entering colonocytes, SCFAs may undergo beta-oxidation and enter the mitochondria, where the citric acid cycle (also known as the Krebs cycle) generates energy for the cell. Another mechanism involves SCFAs binding to GPCR, such as GPR43, GPR41, or GPR109A, on the cell membrane of both colonocytes and immune cells. This interaction inhibits downstream signaling pathways, including NF- κ B, Akt, MAPK, and mTOR, while activating the AMPK pathway. Consequently, this regulates gene transcription and translation, leading to inflammation mitigation, oxidative stress reduction, and autophagy enhancement. AKT refers to the activation of a serine/threonine kinase; NF- κ B to nuclear factor- κ B; AMPK to adenosine 5'-monophosphate (AMP)-activated protein kinase; MAPK to mitogen-activated protein kinase; NLRP3 to nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR)-containing proteins (NLR); mTOR to mammalian target of rapamycin. The figure was created using BioRender.com.

4.1.2. Colorectal Cancer

Colorectal cancer (CRC) ranks among the top three causes of cancer-related mortality worldwide, with increasing recognition of the microbiota's contribution to its pathogenesis [159]. Various factors contribute to CRC, including a high-fat diet, stress, antibiotics, synthetic food additives, a sedentary lifestyle, and environmental factors [160]. High-fat diet, especially prevalent in Western diets featuring high red and processed meat consumption, high fructose corn syrup, and unhealthy

cooking methods, significantly contributes to CRC [161]. Current research has explored the protective role of dietary fibers in reducing the risk of CRC [162,163].

A systematic review and meta-analysis by Alvandi et al. explored the role of fecal SCFAs in CRC incidence and risk stratification [164]. The study, encompassing seventeen case-control and six cross-sectional studies, revealed that individuals with lower concentrations of acetic, propionic, and butyric acid are at a higher risk of CRC. Although these findings suggest a potential association between decreased fecal SCFA concentrations and CRC susceptibility, emphasizing the importance of gut microbiota and bacterial metabolites in CRC prevention, their exact role in CRC prevention remains poorly understood. SCFAs, notably butyrate and propionate, are thought to influence CRC by regulating gene expression, expressing immunomodulatory effects, promoting immune cell differentiation, and mitigating inflammation. Moreover, compelling evidence underscores the role of SCFAs, including butyrate and propionate, in directly influencing intestinal epithelial cell transformation and inhibiting CRC by regulating tumor suppressor gene expression, promoting apoptosis, and modulating CRC cell proliferation and metabolism [165–167]. Butyrate is an energy metabolite and supports normal colon cell proliferation. In CRC cells, butyrate reprograms cell metabolism by promoting pyruvate kinase isozyme 2 (PKM2) activity, inhibiting the Warburg effect and enhancing energy metabolism, therefore inhibiting cancerous colonocytes, which rely on glucose due to the Warburg effect [133,168]. SCFAs act as an HDAC inhibitor, fostering apoptosis in cancer cells [166,169–173]. Additionally, SCFAs play a pivotal anti-inflammatory role in regulating local and systemic immune cells, contributing to their antitumor efficacy [174]. SCFAs mitigate inflammation by inhibiting NF- κ B activation, decreasing pro-inflammatory cytokine expression like tumor necrosis factor-alpha (TNF- α), promoting anti-inflammatory cytokines such as IL-10, and transforming growth factor-beta, and facilitating the differentiation of naïve T cells into Tregs, thereby dampening immune responses [175]. They promote antimicrobial compound production, neutrophil and macrophage inhibition, Treg activation, and dendritic cell induction of tolerogenic properties [174]. In a recent *in vitro* experiment by Mowat et al. CRC cells treated with SCFAs induced much greater activation of CD8⁺ T cells than untreated CRC cells [175]. Surprisingly, the butyrate-producing bacterium *Fusobacterium nucleatum* does not consistently inhibit colon cancer; instead, it may promote cancer progression via mechanisms such as TLR4/myeloid differentiation primary response 88 (MYD88)/NF- κ B signaling [176]. Furthermore, despite the anticipated decrease in DNA damage within cancer cells, numerous reports suggest that SCFAs might exacerbate DNA damage accumulation in CRC cells by disrupting DNA repair mechanisms [173,177–180]. Hence, the antitumorigenic effects of SCFAs likely involve intricate mechanisms extending beyond the tumor cells themselves, particularly significant in CRC cells with underlying DNA repair defects, such as microsatellite instability-high (MSI) CRC subset known for its heightened immunogenicity. Given inflammation's potent role in tumor progression, these effects likely contribute to SCFAs' antitumor efficacy. However, as tumor-targeted T-cell responses are crucial for antitumor immunity and treatment efficacy, SCFAs like butyrate may suppress such responses, potentially fueling tumor progression and compromising treatment outcomes [181–184].

Tian et al. investigated the potential protective role of SCFAs in the development of colitis-associated CRC using a mouse model induced by azoxymethane (AOM) and dextran sodium sulfate (DSS) [185]. The researchers administered a mix of SCFAs in the drinking water throughout the study. They found that the SCFA mix significantly reduced tumor incidence and size in the mice with colitis-associated colorectal cancer. Additionally, the SCFA mix improved colon inflammation and disease activity index score and suppressed the expression of proinflammatory cytokines such as IL-6, TNF- α , and IL-17. These findings suggest that SCFA mix administration could prevent tumor development and attenuate colonic inflammation, indicating its potential as an agent for the prevention and treatment of colitis-associated colorectal cancer. Further investigation is warranted to determine if supplementing with dietary butyrate or consuming foods rich in butyrate-producing bacteria, such as omega-3 polyunsaturated fatty acids, can effectively hinder colorectal cancer and lower its occurrence.

4.1.3. Disorders of the Gut-Brain Axis

The gut-brain axis facilitates bidirectional communication between the gastrointestinal and nervous systems through a complex signaling pathway network [186–188]. This intricate system

encompasses connections such as the enteric nervous system, vagus nerve, immune system, endocrine signals, microbiota, and metabolites. Disruption of communication along the gut-brain axis is increasingly recognized as a significant contributor to neuroinflammation, which is considered a common feature of several neurodegenerative diseases, including Alzheimer's and Parkinson's diseases, characterized by chronic and debilitating conditions marked by the progressive degeneration of neurons [189–195]. Recent research suggests that neurodegenerative diseases may originate in the intestinal epithelium before affecting the brain via the gut-brain axis [196–201]. Various studies have documented the accumulation of protein aggregates, characteristic pathologies of neurodegenerative diseases such as Alzheimer's and Parkinson's, in enteric neurons or the gastrointestinal epithelium years before their detection in the central nervous system [194,202–205]. Functional studies illuminate major microbiota components' roles in the gut-brain axis [206–209]. An important aspect is the observed close correlation between alteration in the microbiota, mucosal immunity, and intestinal vascular impairment, potentially leading to the gradual release of systemic inflammatory mediators and bacterial components such as LPS, thereby initiating or exacerbating the development of neurological disorders [210–212]. Evidence suggests that microbial and systemic inflammatory molecules could contribute to cerebral vascular impairment, microglial activation, neuronal dysfunction, and pre- and post-synaptic activity imbalances. The microbiome of patients with Parkinson's and Alzheimer's disease exhibits a reduction in SCFA-producing bacteria [210,213]. Recent research has highlighted their importance for learning and memory, with cuts in SCFAs associated with inflammation in Multiple Sclerosis patients and compromised neuronal function in various neurodegenerative diseases [214,215]. Furthermore, SCFAs appear to have neuroprotective roles, affecting the brain indirectly or directly by acting as ligands for GPCRs or as epigenetic modulators of HDAC to control transcriptional changes that affect neuronal functions [216–220]. The diminished concentration of SCFAs is suggested to be a critical factor in disrupting gut-brain balance, but the role of SCFA in this context is under active investigation. These SCFAs can cross the blood-brain barrier, likely through the monocarboxylate transport system, influence brain function, and regulate blood flow, with dietary butyrate demonstrating an anti-inflammatory effect in the brain by influencing blood-brain barrier permeability [221,222]. SCFAs have also been implicated in maintaining gut and immune homeostasis in mammalian systems, highlighting their neuro-immunoendocrine regulatory role in the brain [221,223]. In Parkinson's disease, the decline in butyrate levels is thought to lead to intestinal barrier integrity impairment, release of LPS and other pro-inflammatory molecules into the bloodstream, and trigger microglial activation [135,224]. Furthermore, reduced SCFAs and microbiota alterations result in decreased circulating GLP-1 levels. The lowered SCFA-mediated secretion of GLP-1 may activate pro-inflammatory pathways and depressive symptoms in PD patients [225,226]. Additionally, butyrate can induce epigenetic modifications in the genome of neurodegenerative disorder patients. Methylation analysis on blood samples from Parkinson's disease patients and controls revealed a correlation between alterations in butyrate-producing bacterial taxa and epigenetic changes in genes containing butyrate-associated methylation sites. Notably, these modified sites coincide with genes implicated in psychiatric and gastrointestinal disorders [227].

In a study by Kong et al., 16S ribosomal RNA gene sequencing and gas chromatography-mass spectrometry analyses in a *Drosophila* model of Alzheimer's disease revealed a decrease in *Lactobacillus* and *Acetobacter* species correlating with a dramatic reduction in acetate [228]. Similarly, in *Drosophila* models of Parkinson's disease, administration of sodium-butyrate reduced degeneration of dopaminergic neurons and improved locomotor defects in a pan-neuronal transgenic fly model expressing mutant-human- α -Synuclein [222]. The SCFA composition derived from microbes also clinically correlates with neural activity and brain structure, as evidenced by functional and structural magnetic resonance imaging [229]. Recently, Muller et al. examined the fecal SCFA profile of patients with a major depressive disorder/generalized anxiety disorder, comparing it with nuclear magnetic resonance spectroscopy and self-reported depressive and gut symptoms. The severity of depressive symptoms positively correlated with acetate levels and negatively correlated with butyrate levels [230]. In preclinical studies focusing on Alzheimer's disease, prebiotic and probiotic supplementation appear advantageous, although limited data is available specifically on SCFA. Bonfili et al. demonstrated the positive impacts of SLAB51 treatment on 8-week-old transgenic Alzheimer's disease model mice over four months [231–233]. SLAB51 administration enhanced

performance in the novel object recognition test, reduced brain damage, decreased A β plaques, elevated SCFAs, and lowered plasma cytokine levels [233]. Additionally, prebiotics have shown efficacy in Alzheimer's disease amyloid models. Liu et al. treated 5XFAD transgenic Alzheimer's disease model mice with prebiotic mannan oligosaccharide for eight weeks starting from birth. They observed improvements in cognitive deficits, reduction in A β plaques, decreased oxidative stress, diminished microglial activation, and alterations in the gut microbiome. Interestingly, gut microbiome-induced changes in the brain appeared to be mediated by SCFAs, as supplementation with SCFAs produced similar effects [234]. Finally, a case report demonstrated that FMT improved cognitive function, microbiota diversity, and SCFA production in an Alzheimer's patient [235].

Several studies have investigated the administration of probiotics in both murine models and human subjects with Parkinson's disease, exploring their impact on gastrointestinal and neurological symptoms [236–242]. A pilot study regarding FMT use in Parkinson's patients has recently been published, with promising data [243]. However, only a few studies have evaluated SCFA's role. Specifically, *Bifidobacterium* has been demonstrated to be effective in modulating the host microbiota in a murine model induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [244]. In mice overexpressing α -synuclein, a prebiotic diet altered the activation of microglia and motor deficits by changing the composition of the gut microbiome and levels of SCFAs [245]. Combining polymannuronic acid with *Lactocaseibacillus rhamnosus* GG demonstrated more potent neuroprotective effects against Parkinson's disease than either treatment alone, suggesting the therapeutic promise of synbiotics in Parkinson's disease [246]. Oral administration of *B. breve* CCFM1067 to MPTP-induced Parkinson's disease mice led to a reduction in intestinal microbial alterations, marked by a decline in pathogenic bacteria (*Escherichia-Shigella*) and an increase in *Bifidobacterium* and *Akkermansia*. This intervention also restored SCFA production (butyrate and acetate), which may account for the observed local and cerebral anti-inflammatory effects. Recently, *Bifidobacterium animalis* subsp. *Lactic* Probio-M8 (Probio-M8) was examined to evaluate its additional beneficial effects and mechanisms when used as an adjunct treatment alongside conventional therapy (Benserazide and dopamine agonists) in patients with Parkinson's. This investigation was conducted over three months in a randomized, double-blind, placebo-controlled trial [247]. Clinical outcomes were assessed by analyzing changes in various clinical indices, gut microbiome composition, and serum metabolome profiles before, during, and after the intervention. The findings revealed that co-administration of Probio-M8 resulted in additional benefits, including improved sleep quality, reduced anxiety, and alleviated gastrointestinal symptoms. Metagenomic analysis demonstrated significant modifications in the participants' gut microbiome and serum metabolites following the intervention. The serum concentration of acetic acid was notably higher in the probiotic group.

IBS is a Disorder of Gut-Brain Interaction (DGBI) characterized by abdominal pain and changes in stool consistency or frequency. According to the Rome IV criteria, IBS can be divided into four subtypes based on the primary clinical features: IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), IBS with mixed stool patterns (IBS-M), and unclassified IBS [248–250]. SCFAs play a pivotal role in IBS, with reported findings indicating that patients with IBS exhibit significantly elevated levels of acetate, propionate, and total SCFAs in fecal samples, with the severity of symptoms correlating positively [251]. Alterations in SCFA levels are subtype-specific, with reduced levels in IBS-C and increased levels in IBS-D compared to controls [252,253]. Treem et al. sought to investigate whether patients with IBS-D exhibit a distinct pattern and pace of carbohydrate and fiber fermentation in SCFA in vitro studies of fecal homogenates compared to controls. The fecal SCFA profile of IBS-D patients revealed diminished concentrations of total SCFA, acetate, and propionate alongside elevated levels and proportion of n-butyrate [254]. Fredericks et al., in 2021, examined gut microbiota, concentrations of SCFA, and mRNA expression of monocarboxylate transporters in individuals with IBS-C, IBS-D, and healthy controls. They observed changes in fecal SCFA ratios in both IBS groups, with a decrease in all three measured SCFAs in IBS-C and a reduction specifically in acetic acid in IBS-D [255]. Similarly, Undseth et al. aimed to compare colonic fermentation between individuals with IBS and healthy counterparts by examining serum SCFA concentrations before and 90 minutes after ingesting lactulose, an unabsorbable yet fermentable carbohydrate. They found that reduced serum SCFA levels post-lactulose ingestion may indicate compromised colonic fermentation in IBS patients [256]. The dysregulated SCFA levels in feces are linked to shifts in intestinal bacterial composition in IBS patients, characterized by higher counts of acetate and propionate-producing

bacteria like *Veillonella* and *Lactobacillus* and lower counts of butyrate-producing bacteria like *Roseburia-Eubacterium* rectale group [251,257,258]. Zhou et al. recently set out to investigate how linacotide affects the gut microbiota and pinpoint essential bacterial genera that could influence linacotide's effectiveness. Interestingly, they discovered a direct link between higher levels of *Blautia* and SCFA concentrations and the amelioration of clinical symptoms in patients with IBS-C [259].

SCFAs, particularly propionate and butyrate, show promise as non-invasive biomarkers for diagnosing IBS, with diagnostic properties consistent across all IBS subgroups. Farup et al. 2016 examined fecal SCFA as a potential diagnostic indicator for IBS in a study involving 25 IBS subjects and 25 controls. They assessed total SCFA levels and individual SCFA amounts to identify the most effective diagnostic approach. Their findings revealed that the discrepancy between propionic and butyric acid levels demonstrated superior diagnostic performance using a threshold of 0.015 mmol/l to indicate IBS, independent of the IBS subgroup [260].

Several potential mechanisms exist through which SCFAs could influence the pathophysiology of IBS, many of which have been previously examined in the IBD section of this review. As already described, SCFAs interact with specific receptors, such as GPR41, GPR43, and GPR109A, expressed in various gastrointestinal cell types, modulating physiological responses. They play a multifaceted role in immunity and inflammation, influencing inflammatory mediator production, immune cell differentiation, and intestinal barrier integrity [261–265]. Additionally, SCFAs influence the differentiation of immune cells, including T cells and Tregs, and suppress intestinal inflammation [145,266,267]. They also contribute to the integrity of the intestinal barrier by promoting mucin secretion and enhancing tight junction assembly [268–273].

Furthermore, SCFAs impact gut motility through various mechanisms, including modulation of neural activity, neurotransmitter release, and regulation of calcium signaling and smooth muscle contractility [274–285]. The effects of SCFAs on colonic motility are nuanced and context-dependent, varying based on SCFA concentration and colonic segment [274–285]. Waseem et al., in their recent prospective observational study, investigated the associations between fecal SCFAs, colonic transit time, fecal bile acids, and dietary intake in individuals with IBS and healthy controls [286]. They found that fecal SCFAs were inversely correlated with overall and segmental colonic transit time, with similar patterns observed in both IBS and healthy control groups. Additionally, the acetate-to-butyrate ratio was associated with slower transit times. Logistic regression analyses demonstrated that acetate could accurately predict delayed colonic transit time and BAD. These findings suggest that fecal SCFAs and dietary factors may play a role in the IBS pathophysiology and serve as diagnostic markers for bowel transit disorders [286].

4.2. Metabolic Diseases

Metabolic diseases, spanning conditions like obesity, type 2 diabetes (T2D), and metabolic dysfunction-associated steatotic liver disease (MASLD), present significant health challenges globally [287–289]. Central to the pathophysiology of these conditions is the intricate interplay between the gut microbiota and SCFAs, which profoundly influence host metabolism. An imbalance in gut microbial communities is a critical contributor to the development of common metabolic disorders in humans [290]. Nevertheless, the emerging evidence underscores the promising therapeutic potential of targeting the gut microbiota and its metabolites for managing various metabolic conditions, extending beyond the well-established associations with obesity, T2D, and MASLD. Mechanisms of SCFA in metabolic disorders are summarized in Table 6.

Table 6. Mechanisms of SCFA in metabolic diseases.

Disease	Supposed Mechanisms of SCFA Protection/Risk
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Obesity		1. Appetite Regulation: SCFAs can stimulate the release of Peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) from gut endocrine cells. These hormones act centrally in the hypothalamus to signal satiety and decrease appetite.
		2. Fat Storage and Metabolism: Increased SCFA-mediated adipocyte activity might favor fat storage in subcutaneous adipose tissue. SCFAs might enhance brown adipose tissue (BAT) activity, promoting thermogenesis and potentially increasing energy expenditure.
		3. Metabolic effects: SCFAs activate GPR41 and GPR43 receptors on fat and immune cells, potentially influencing insulin sensitivity, fat metabolism, inflammation, and, thus, weight regulation.
Type 2 diabetes		1. Effects on glucose metabolism: SCFAs act as secretagogues for hormones like GLP-1 and PYY, which enhance satiety and decrease appetite. GLP-1 enhances insulin secretion from the pancreas and reduces glucagon secretion, lowering blood sugar levels. In the liver, SCFAs inhibit glycolysis and gluconeogenesis, promoting glycogen synthesis and fatty acid oxidation. In skeletal muscle and adipose tissue, they improve glucose uptake and glycogen synthesis.
		2. Role in intestinal gluconeogenesis (IGN): SCFAs promote IGN production, which is crucial for glucose and energy homeostasis.
		3. Gut Health: SCFAs promote a healthy gut environment, which may be linked to a lower risk of developing diabetes.
Metabolic dysfunction-associated steatotic liver disease		1. Improved Insulin Sensitivity: SCFAs can activate GPR43 on adipocytes and hepatocytes. GPR43 activation can stimulate insulin signaling pathways, leading to increased glucose uptake by these cells and potentially improving overall insulin sensitivity. SCFAs might also suppress gluconeogenesis in the liver.
		2. Anti-inflammatory Effects: SCFAs can modulate the activity of immune cells like macrophages in the liver. They might suppress pro-inflammatory cytokine production (e.g., TNF-α, IL-6) and promote the activity of regulatory T cells, creating an anti-inflammatory environment. SCFAs inhibit the NF-κB signaling pathway, a key player in inflammatory responses.
		3. Gut-Liver Axis: SCFAs might also influence Fibroblast Growth Factor (FGF) signaling pathways in the gut-liver axis, potentially impacting bile acid metabolism and hepatocyte function. SCFAs might stimulate the enterohepatic circulation of bile acids. SCFA-mediated bile acid signaling can activate FXR, a

nuclear receptor in the liver, potentially influencing hepatic lipid metabolism and reducing steatosis.

4.2.1. Obesity

Obesity poses a significant risk for various chronic conditions, including T2D, insulin resistance, MASLD, and cardiovascular disease, among others [291]. Interestingly, obese individuals have been associated with altered fecal SCFA concentrations, particularly propionate. A study involving Mexican children revealed that those with excess weight and obesity exhibited lower concentrations of fecal propionate and butyrate compared to their normal-weight counterparts [292]. A recently published study examined African-origin groups from different regions and discovered variations in gut microbiota composition and predicted functions linked to population obesity and geography [293]. The study found that fecal SCFA concentrations are inversely correlated with microbial diversity and obesity. However, the prediction of obesity from microbiota varied by country: Prevotella-rich microbiota dominates in traditionally non-western groups, while Bacteroides-rich microbiota is found in high-income countries. Conversely, other studies have associated obese individuals with higher fecal SCFA concentrations than lean individuals [294,295]. A study in the Netherlands found that overweight and obese individuals had elevated fecal SCFA concentrations compared to lean counterparts, suggesting enhanced microbial energy extraction [294]. Indeed, a previous survey of 441 adults published by Cuesta-Zuluaga et al. in 2018 revealed a correlation between higher fecal SCFA levels and obesity [296]. The excessive production of SCFA may contribute to weight gain due to increased energy storage despite its typically beneficial effects on well-being [294,297–300].

However, these findings are debatable due to possible fluctuations in SCFA concentrations and broader microbiota alterations within the intestinal microbial community [301]. Numerous studies have investigated the role of SCFAs in adiposity, examining human subjects and conducting in vitro and in vivo animal studies. In vitro studies have demonstrated that acetate and propionate treatment can induce expressions of vital metabolic regulators, promoting lipolysis metabolism [302,303].

Animal studies have shown that SCFA supplementation can counteract weight and adiposity gain, with treatments like sodium butyrate inducing weight loss by enhancing energy expenditure and fat oxidation [304,305]. In mice on a high-fat diet, butyrate supplementation increases the expression of peroxisome proliferator-activated receptor- γ (PPAR γ) coactivator-1 alpha (PGC-1 α), activates AMP Kinase (AMPK) and p38, and improves insulin sensitivity inducing weight loss by enhancing energy expenditure and fat oxidation [306]. This finding was observed when the functioning of adipose and hepatic PPAR γ pathways were intact. Dietary supplementation with SCFAs has been found to upregulate GPR43 and GPR41 expressions in adipose tissue, enhance triglyceride hydrolysis, promote free fatty acid oxidation in adipose tissue, leading to brown fat production, and reduce body weight in HFD-fed mouse models [307]. *Ganoderma lucidum*, a medicinal mushroom with a long history of use in Asian countries, has been shown to increase SCFA production and GPR43 expression in C57BL/6 J mice, enhance ileal tight junction proteins and antibacterial peptides expression, mitigate endotoxemia, and attenuate HFD-induced upregulation of TLR4/Myd88/NF- κ B signaling in adipose tissue [308,309].

Overall, while growing evidence supports the role of SCFAs in obesity treatment, comprehensive mechanistic studies are needed to elucidate their precise mechanisms of action and optimize their therapeutic potential.

4.2.2. Type 2 Diabetes

Research involving individuals from various ethnic backgrounds has revealed that those with T2D exhibit diminished levels of SCFA-producing bacteria. This is implicated in insulin resistance and the progression of T2D and can contribute to gut inflammation [310].

Regarding microbial metabolites, SCFAs exhibit diverse effects across various sites regulating glucose metabolism. In vitro and in vivo studies have shown that SCFAs act as potent secretagogues for glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), thereby enhancing feelings of satiety via the gut-brain axis. Consequently, they may indirectly decrease appetite and subsequent food intake, thus mitigating the risk of weight gain, a known predisposing factor for T2D [218]. Research has revealed that acetate can reduce hormone-sensitive lipase phosphorylation in human multipotent adipose tissue-derived stem adipocytes in a Gi-coupled manner [311]. Acetate and butyrate activate GPR43 and GPR41 on rat intestinal cells, stimulating insulin, GLP-1, and peptide YY secretion, modulating blood lipid metabolism and lowering peripheral blood glucose levels, slowing intestinal transit, decreasing gastric emptying, food intake, and intestinal motility [312]. Acetate and butyrate activate GPR43 and GPR41 receptors on intestinal cells, promoting the secretion of insulin, GLP-1, and peptide YY, which helps modulate blood lipid metabolism and lower peripheral blood glucose levels [313,314]. In the liver, SCFAs have been observed to inhibit glycolysis and gluconeogenesis while enhancing glycogen synthesis and fatty acid oxidation [218,315–317]. Additionally, SCFAs have been shown to improve glucose uptake in skeletal muscle and adipose tissue by upregulating the expression of GLUT4 through AMPK activation. Furthermore, in skeletal muscle, SCFAs reduce glycolysis, leading to the accumulation of glucose-6-phosphate and increased glycogen synthesis [306,315–320]. In preclinical models, ingesting soluble dietary fibers prompts the production of SCFAs, particularly propionate, and butyrate, which activate intestinal gluconeogenesis (IGN), a process crucial for glucose and energy homeostasis [321]. SCFAs play a role in promoting IGN production to mitigate metabolic diseases in mice [322]. Butyrate triggers IGN gene expression via a cAMP-dependent mechanism. At the same time, propionate, as an IGN substrate, enhances gene expression through activation of the gut-brain neural circuit [321], thereby exerting beneficial effects on glucose regulation, energy balance, and body weight control. In rabbits, acetate could curb lipid accumulation, promoting lipolysis and fatty acid oxidation and inhibiting synthesis [323].

Regarding the microbiota populations, T2D patients exhibit a higher abundance of *Proteobacteria* and a skewed *Firmicutes/Bacteroidetes* ratio compared to healthy individuals, alongside reduced SCFA-producing *Bacteroides* [324–326]. Acetate and butyrate improved intestinal barrier function and increased the number of *Bacteroides* species in NOD model mice, which helped to inhibit T1D [327].

As a result of the role of SCFAs in human glucose metabolism, intervention studies involving the supplementation of propionate and butyrate have been conducted. A recent meta-analysis has shown that probiotic intervention can significantly improve the homeostatic model assessment of insulin resistance (HOMA-IR) and considerably decrease glycated hemoglobin HbA1c levels and fasting blood glucose levels in T2DM patients compared to placebo [328,329]. However, the evidence remains inconclusive due to the limited number of studies conducted in small cohorts. Nevertheless, these studies suggest that inulin-propionate supplementation (10 g/day) increases GLP-1 and PYY levels while reducing food intake, contributing to body weight regulation [330,331]. Additionally, sodium butyrate supplementation (4 g/day) enhances insulin sensitivity solely in lean individuals and not those with metabolic syndrome [332]. Despite these promising findings, the optimal doses and exposure durations for SCFA treatment in T2D remain undefined, and further research is needed to elucidate their time- and dose-dependent effects. Additionally, studies have focused on translating fecal microbiota from lean donors to recipients with metabolic syndrome to enhance insulin sensitivity [333,334].

Moreover, adopting a low-calorie, low-protein, low-carbohydrate HFD as a fast-mimicking diet has shown promise in promoting cell regeneration, reducing protein kinase A and mTOR activity, inducing the expression of Sox2 and Ngn3, and restoring insulin production, secretion, and glucose homeostasis in both T2D mouse models and type 1 diabetes patients [335].

4.2.3. Metabolic Dysfunction–Associated Steatotic Liver Disease

The transition from NAFLD to MAFLD and MASLD marks a significant shift in the understanding and classification of metabolic liver diseases, aiming to reflect their pathophysiology better and reduce social stigma [289]. This evolution in terminology and diagnostic criteria, supported by international experts and widely accepted in clinical practice guidelines, emphasizes the link between metabolic dysfunction and liver health, paving the way for improved disease identification and management strategies. The connection between MASLD and its advancement to steatohepatitis and cirrhosis has previously been associated with the gut microbiome via multiple pathways. This correlation could stem from gut microbiota alterations and the systemic impact of metabolites derived from it, such as SCFA [336].

Notably, the gut microbiota of patients with the formerly known non-alcoholic fatty liver disease (NAFLD) exhibits a significantly reduced abundance of SCFA-producing bacteria such as *Bacteroides*, *Lactobacillus curvatus*, and *L. plantarum* [337–340]. As described in this review, previous studies have suggested that individuals with obesity and MASLD tend to have higher levels of fecal SCFAs [294,296,341]. However, it is unclear whether there is a relationship between circulating SCFA levels and MASLD and other metabolic disorders [298,342–344]. While some studies have found no significant differences between control groups and MASLD patients, others have reported lower SCFA levels in MASLD cirrhosis or higher levels in patients with hepatocellular carcinoma and cirrhosis linked to MASLD [342,344–346]. These conflicting conclusions may result from differences in study design, such as variations in the selection criteria for control and MASLD patients or discrepancies in the severity of underlying MASLD conditions.

The mechanisms linking SCFAs and MASLD may involve alterations in glucose homeostasis, lipid metabolism, and inflammatory and immune responses [341,347]. The gut-liver axis plays a crucial role in this process, as evidenced by the reciprocal relationship between gut microbiota, gut-derived metabolites, and liver function [348].

Although the precise role of these SCFAs in MASLD remains unclear, insights may be gleaned from research on other metabolic disorders as previously described in this review. Previous studies have associated acetate with greater gut microbiota diversity, reduced visceral fat, and less severe MASLD cases [349,350]. Consistent with these findings, our study observed lower acetate levels in MASLD patients than healthy controls. Propionate, when present in adequate concentrations, is also linked to positive health outcomes and the regulation of gut hormones influencing appetite and fullness [350]. However, conflicting evidence exists, as evidenced by a study on early MASLD patients where higher levels of SCFA-producing bacteria and fecal acetate and propionate were associated with an elevated TH17/Treg ratio, suggesting a potential contribution to low-grade inflammation [341].

In a recent study, Thing et al. investigated the association between plasma SCFAs and MASLD. The results showed higher plasma concentrations of propionate, formate, valerate, and α -methylbutyrate but lower plasma acetate concentrations in MASLD patients compared to healthy controls. Moreover, among MASLD patients, significant fibrosis was positively associated with several SCFAs [351].

Animal studies have shown that supplementation with SCFAs such as sodium acetate and sodium butyrate can protect against hepatic steatosis induced by nicotine and metabolic factors [352,353]. In MASLD patients, downregulation of the GLP-1 receptor in the liver is observed, with butyrate supplementation in MASLD mice enhancing GLP-1 receptor expression by inhibiting HDAC-2, consequently promoting energy metabolism and inhibiting lipid accumulation [354]. Butyrate also improves insulin sensitivity, activates AMPK to induce the expression of fatty acid oxidation genes in hepatocytes, and reduces fat deposition in MASLD mice [355]. The MASLD mouse model increases the abundance of beneficial bacteria in the intestine, such as *Christensenellaceae*, *Blautia*, and *Lactobacillus*, establishing a positive feedback loop by augmenting butyric acid production [356,357]. Additionally, butyrate attenuates MASLD-induced intestinal mucosal injury by upregulating ZO-1 expression in the intestinal tract of mice, thereby preventing enterotoxin migration to the liver and suppressing liver inflammation [358].

Overall, these findings underscore the therapeutic potential of SCFAs in preventing and managing MASLD by targeting multiple pathways involved in its pathogenesis. Emerging evidence

underscores the pathogenic role of microbe-derived metabolites, including trimethylamine, secondary bile acids, SCFAs, and ethanol, in MASLD pathogenesis [348].

4.3. Therapeutic Implications

4.3.1. Fecal Microbiota Transplantation

FMT is a therapeutic approach involving the transfer of a fecal suspension from a healthy donor to the patient's gastrointestinal tract to restore average microbial composition and function [359,360]. It is recommended by guidelines and consensus from international societies for the treatment of recurrent *Clostridioides difficile* infection (rCDI) [361–365]. Encouraging results indicate that FMT might also potentially treat additional conditions linked to disruptions in gut microbiota composition, including IBD and disturbances of the gut-brain axis, like anorexia [359,361,366–372]. The efficacy of FMT largely depends on the donor's microbiota, with "super donors" possessing favorable bacterial characteristics crucial for successful outcomes [373]. Advancements in frozen stool processing have facilitated the establishment of FMT libraries for clinical applications [369,374]. However, the specific bacterial composition of FMTs and the underlying treatment mechanisms remain unclear, necessitating further research to better understand this promising therapeutic approach [375].

Metabolite levels linked to gut microbiota, including SCFAs and bile acids, show improvement following FMT. Paramsothy et al. found that patients with UC achieving remission after FMT exhibited enrichment of *Eubacterium hallii* and *Roseburia inulinivorans*, along with elevated levels of SCFA biosynthesis and secondary bile acids, compared to non-responders [376]. FMT administration is thought to elevate SCFA levels in the colon and regulate the NF- κ B pathway to reduce inflammation [377,378]. In a study conducted by Osaki et al. in 2021, the effectiveness of FMT was evaluated along with its impact on fecal microbiota and SCFA levels in patients with IBD and rCDI. The analysis of fecal microbiota showed changes in bacterial composition after FMT, with modifications in specific bacterial taxa associated with clinical response. In UC patients, fecal SCFA levels remained unchanged post-FMT, regardless of treatment response. However, responders showed a significant increase in fecal butyric acid levels in CD patients at eight weeks post-FMT compared to donors, while rCDI patients had lower pre-FMT butyric acid levels than donors. Furthermore, fecal propionic acid levels significantly increased at eight weeks post-FMT in rCDI patients, while acetic acid and butyric acid levels showed a non-significant increase [379]. Conversely, Seekatz et al. observed increased butyrate, acetate, and propionate levels and recovery of secondary bile acids like deoxycholate and lithocholic in rCDI patients post-FMT [380].

A 2021 RCT conducted by El-Salhy and colleagues investigated the impact of FMT on fecal SCFA levels in patients with IBS. The study included 142 participants from a previous study. The results showed that individuals who received FMT had increased levels of butyric acid, especially in the 30-g and 60-g FMT groups. In addition, the 60-g FMT group had higher levels of total SCFAs and several other SCFA types. Significantly, higher butyric acid levels were associated with symptom improvement in FMT responders [381].

4.3.2. Dietary Intervention

Dietary composition exerts a significant influence on gut microbes [382,383]. Various diets can alter microbial composition, increase the ratio of harmful bacteria to beneficial metabolites, and contribute to the development of chronic metabolic diseases such as obesity and T2D [384,385]. The potential role of dietary interventions in diseases from cognitive impairment to IBD has brought new studies on the connection between diet and microbiota [386–388]. Adopting healthy eating habits with a diet rich in fresh fruits, vegetables, and whole grains can reduce the risk of cardiovascular and metabolic diseases and cancer. On the other hand, consuming refined and processed foods such as sugary treats, fried foods, processed meats, and refined grains may increase their likelihood [385,389].

Dietary fiber is an essential component of food, and soluble fiber is resistant to gastrointestinal digestive enzymes and is utilized by the anaerobic intestinal microbiota to produce SCFAs [390]. In a recent systematic review examining the impact of dietary fibers on SCFA production and gut microbiota composition in healthy adults, a total of forty-four human intervention studies on confirmed and candidate prebiotics were included. Among them, inulin was the most extensively studied dietary fiber. While specific studies indicated notable rises in total SCFAs after dietary fiber intervention, others observed no significant alterations, indicating that the influence of nutritional

fibers on SCFA levels may be influenced by variables such as dosage, fiber type, and baseline gut microbiota composition [391,392]. To analyze the potential mechanisms of the role of the ketogenic diet in epilepsy, a recent study by Gudan et al. examined the impact of this on the synthesis of intestinal SCFAs in healthy adults [393]. The analysis highlighted that cruciferous and leaf vegetables, berries, and nuts consumption on a ketogenic diet have been linked to a positive impact on the profile of SCFAs. The LIBRE trial investigated the effect of the Mediterranean diet in 260 women and found that adherence to the Mediterranean diet led to increased fecal SCFA levels, particularly propionate and butyrate [394].

Dietary fibers play a crucial role in modulating intestinal SCFA levels, preserving mucosal homeostasis, enhancing intestinal epithelial integrity, fostering the growth of Tregs, and suppressing the expression of inflammatory cytokines to prevent or alleviate disease [395]. Supplementation with wheat bran, rich in arabinoxylan oligosaccharides, elevated butyrate, acetate, and propionate levels, along with total SCFA concentrations in a human trial [396]. However, the increased fecal bulking and reduced transit time associated with higher dietary fiber intake could decrease colonic SCFA absorption, potentially explaining the observed rise in fecal SCFA concentrations in studies with increased fiber content.

According to two studies, consumption of barley-kernel-based bread rich in β -glucan fibers for three days can result in an increase in the levels of *Prevotella* and a decrease in the levels of *Bacteroides* and intensified fermentation activity, SCFA serum levels, and gut hormone secretion (GLP-1, PYY, and GLP-2) in healthy adults, enhancing insulin sensitivity [397,398]. These results were observed among healthy participants, and they suggest that certain foods can have a significant impact on the gut microbiome. This shift was linked to a decrease in postprandial glucose response, corresponding to an increase in total serum SCFA concentration. Another study indicated that a supplement containing three grams per day of high molecular weight β -glucan altered the gut microbiota composition, increasing *Bacteroides* and decreasing Firmicutes, with correlations observed between changes in these bacteria and cardiovascular disease risk factors [399]. These findings suggest that high molecular weight β -glucan fibers can induce microbiota shifts, potentially explaining their metabolic benefits.

In 2020, Farup and Valeur conducted a study to investigate the impact of weight-loss interventions on fecal SCFA levels in people with obesity. They studied ninety subjects with morbid obesity and measured their fecal SCFA levels before and after a six-month conservative weight-loss intervention followed by bariatric surgery. The study found a reduction in total fecal SCFA levels post-surgery, accompanied by a decrease in the main straight-chain SCFAs such as acetic-, propionic-, and butyric-acids, and an increase in branched-chain SCFAs like isobutyric-, isovaleric-, and isocaproic-acids. This indicated a shift towards a proteolytic fermentation pattern. Interestingly, SCFA levels were associated with diet but not metabolic markers or fecal microbiota composition. This suggests that dietary interventions can potentially mitigate these effects [400].

4.3.3. Prebiotic and Probiotic Applications

In recent years, there has been a surge of interest in prebiotics and probiotics [401], with their mechanisms of action being intricate and diverse, often specific to particular strains and compounds [402]. Probiotics can alter the gastrointestinal microenvironment, outcompete pathogenic bacteria for nutrients, and hinder pathogenic growth by producing antimicrobial compounds unique to each strain [403,404]. Probiotics' safety and potential roles in diseases where gut microbiota is considered part of the pathophysiology have fueled research in this area [405,406]. SCFAs have the potential to regulate cognitive abilities and influence mental function via the gut-brain axis [407].

In 2015, Sawin et al. investigated the prebiotic properties of glycomacropeptide (GMP), a glycoposphopeptide. Using mouse models, researchers found that GMP reduced the abundance of *Desulfovibrio* bacteria, increased levels of cecal SCFA, and exhibited anti-inflammatory effects compared to casein and amino acid diets [408].

Holmes et al. conducted a six-week, three-period prebiotic intervention study on forty-one healthy adults to analyze personalized responses to different prebiotics, inulin, GOS, and dextrin. They found that the proportional increase in butyrogenic response to prebiotics was inversely correlated with regular dietary fiber intake [409]. The study suggested that individuals' gut

microbiota may have a limited capacity to produce SCFAs from fiber, and their responsiveness to prebiotic treatment could be predicted based on diet and baseline SCFA levels in the stool.

A systematic review and meta-analysis focusing on dietary fiber interventions in individuals with type 2 diabetes revealed improvements in the relative abundance of *Bifidobacterium* and total SCFA. They enhanced glycated hemoglobin levels [410]. This review included an intervention study involving 16 g per day of inulin-type fructans for six weeks, notably increasing bifidobacteria concentrations [411]. Although the prebiotic treatment boosted fecal SCFA concentrations, including total SCFA, acetate, and propionate, it had no discernible impact on butyrate or overall bacterial diversity. Moreover, it did not positively influence glucose levels, insulin, gut hormones, appetite, or energy intake [412,413].

Inulin-type fructans possess a prebiotic effect, elevating *Bifidobacterium*, *Lactobacillus*, and *Faecalibacterium prausnitzii* abundances. The benefits reported include improved intestinal barrier function, insulin sensitivity, lipid profile, mineral absorption, and satiety [413]. However, the effects on blood glucose, cholesterol, and triglyceride concentrations appear favorable primarily in individuals with prediabetes and diabetes [414].

In a randomized, double-blind, placebo-controlled study assessing the impact of the probiotic intervention on fecal SCFAs, a multi-strain probiotic formula was administered to 56 postmenopausal obese women [415]. The study revealed a positive effect on their cardiometabolic health, with the higher probiotic dose group showing elevated levels of fecal SCFAs [415]. Another recent study investigated the impact of a low-carbohydrate diet compared to a habitual diet on fecal SCFA levels and serum inflammatory markers in obese women undergoing an energy-restricted diet [416]. After adjusting for baseline parameters, the two diet groups observed significant differences in fecal levels of butyric, propionic, and acetic acid.

5. Conclusion

A significant disparity has been highlighted in the clinical studies conducted with butyrate compared to those with propionate and acetate. Indeed, propionate and acetate play a secondary role compared to butyrate, although the evidence suggests that acetate and propionate are equally applicable fatty acids as butyrate and that gut bacteria sometimes utilize them to produce butyrate [8,299,302,304,305]. Similarly, it has been noted that the availability of propionate/acetate-based supplements is deficient compared to butyrate-based supplements. An additional emerging idea is that any therapeutic, pharmacological, integrative, or nutritional intervention must consider the role played by the intestinal microbiota. Human health is correlated with the ecology of microbial communities living inside and outside our bodies [417], and health itself evolves within an "ecological" perspective that involves the interaction between living beings and the environment. This important concept has been highlighted by different clinical [418,419] and pre-clinical [392] studies where individual microbiota composition and functions have been reported to influence dietary fiber supplementation, with varying consequences on intestinal health. For this reason, recognizing the importance of focusing on the microbiome leads to a "before" and "after" in health research and innovation, with the perspective nowadays to develop personalized medicine for patients, taking into account individual microbiota features when indicating the most appropriate treatment [361,420]. The relationship between nutrition, production/utilization of SCFA, and variation of the microbiota is just a small example to explain this ecological perspective that is gradually evolving towards the more philosophical concept of One Health, and perhaps in the not too distant future towards the more holistic concept of "Microbiome One Health" [421].

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