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REVIEW

Recent advances in the therapeutic application of short-chain fatty acids (SCFAs): An updated review

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ABSTRACT

Over the past decade, the gut microbiota has emerged as an important frontier in understanding the human body's homeostasis and the development of diseases. Gut flora in human beings regulates various metabolic functionalities, including enzymes, amino acid synthesis, bio-transformation of bile acid, fermentation of non-digestible carbohydrates (NDCs), generation of indoles and polyamines (PAs), and production of short-chain fatty acids (SCFAs). Among all the metabolites produced by gut microbiota, SCFAs, the final product of fermentation of dietary fibers by gut microbiota, receive lots of attention from scientists due to their pharmacological and physiological characteristics. However, the molecular mechanisms underlying the role of SCFAs in the interaction between diet, gut microbiota, and host energy metabolism is still needed in-depth research. This review highlights the recent biotechnological advances in applying SCFAs as important metabolites to treat various diseases and maintain colonic health.

KEYWORDS

Nutrition; intestinal microflora; short-chain fatty acids (SCFAs); molecular response; pathogenesis; colonic health; metabolic disorders

Introduction

Human beings' intestinal tract is densely populated with various microorganisms, and their composition is a vital determining factor for human health and disease. Though, the multifaceted nature of the connection among the microbial cells and their host is quite challenging in explicating the role of gut microbiota in human health (Holmes et al. 2011). Various recent studies have demonstrated gut microbiota's role in the metabolism of several medicinal and food ingredients. Over the last decade, the gut microbiota has emerged as an important frontier in understanding the human body's homeostasis and the development of diseases. Gut flora in human beings regulates various metabolic functionalities like production of short-chain fatty acids (SCFAs), synthesis of amino acids (AAs), bio-transformation of bile acid, fermentation of NDCs, generation of indoles and polyamines (PAs) (Nicholson et al. 2012; Postler and Ghosh 2017; Putignani et al. 2016).

Gut flora contains diverse microorganisms that play an essential role in various nutritional, immunological, and

metabolic functionalities (Fang et al. 2020). SCFAs are microbial metabolites reported to be responsible for maintaining the immune homeostasis of the central nervous, urinary and respiratory systems (Ratajczak et al. 2019). Intestinal and extra-intestinal ailments, including inflammatory bowel disease, neuropathology, allergy, diabetes, & obesity, are developed when misbalance occurs between gut microbiota and gastrointestinal tract (Holmes et al. 2011; Putignani et al. 2016). Scientists are shifting toward exploring gut microbiota due to their composition toward propagating and developing numerous diseases. Among all the metabolites produced by gut flora, SCFAs receive lots of attention from scientists due to pharmacological and physiological characteristics associated with them (Figure 1). SCFAs are metabolites having a significant association between inflammatory response and gut microbiota. These are classified as vital metabolic products resulting from bacterial fermentation of NDCs entering the colon (Le Poull et al. 2003; Nilsson et al. 2006; Puddu et al. 2014).

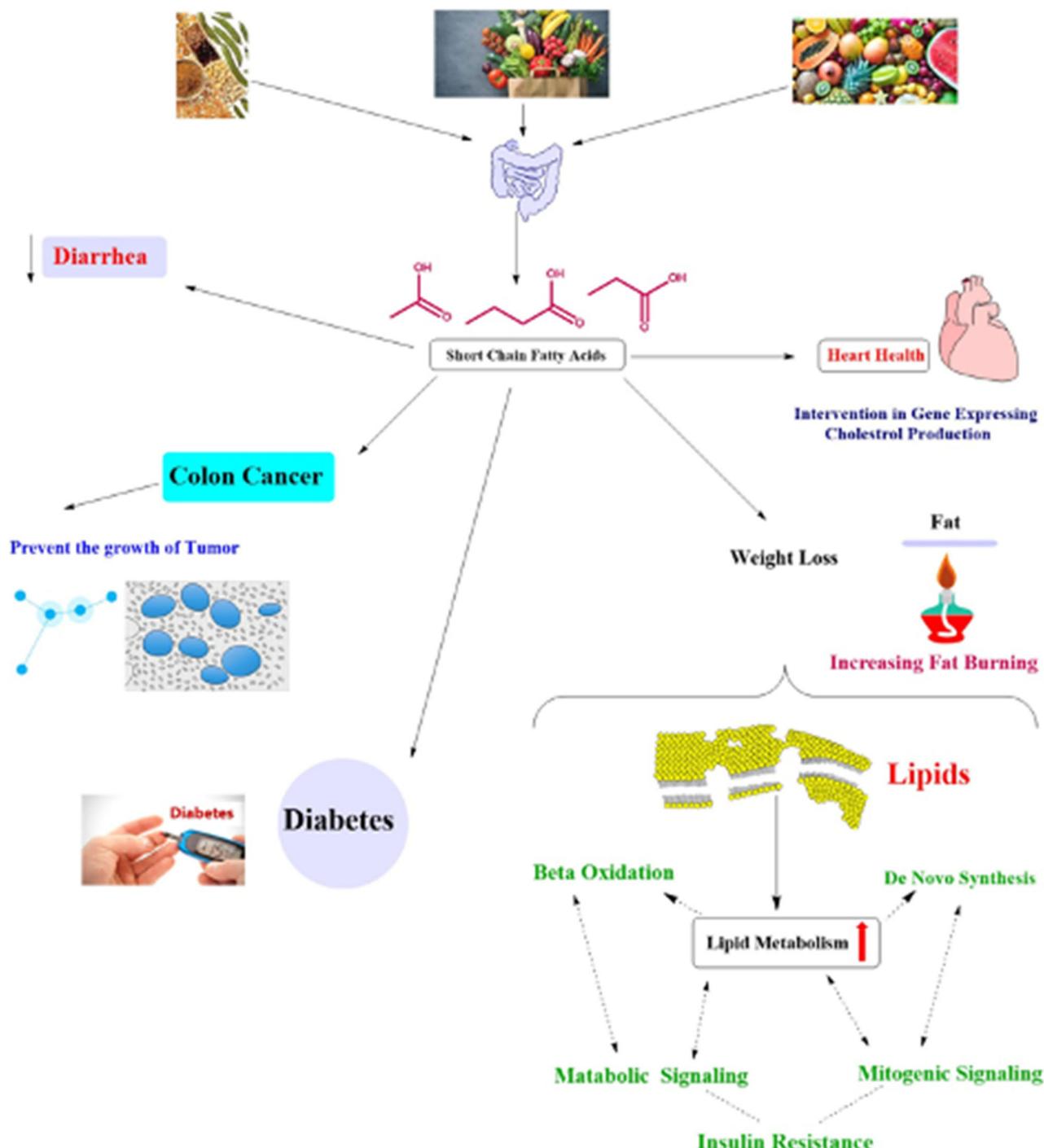


Figure 1. Scheme of functional properties of short-chain fatty acids (SCFAs).

The primary functionality of gut flora is the fermentation of macro-fibrous food material into SCFAs. This fermentation predominantly produces acetate, propionate, and butyrate. For the generation of SCFAs, dietary fibers are considered the most effective substrates (Den Besten et al. 2013). Various factors like gut transit time, pH of the colon, source of the substrate, quantity & composition of gut flora affects the type, rate, and abundance of SCFAs produced. SCFAs can contribute up to 10% of human beings' total caloric requirements depending upon the factors mentioned above. SCFAs play an essential part in maintaining the overall colonic health as they are promptly produced and

absorbed in the colon (van der Beek et al. 2017). Among all the produced SCFAs, butyrate is the most vital one in maintaining colonic health, as it directly acts as a source of energy for colonocytes (epithelial cells of the colon). Nearly all the butyrate produced is taken up by the colonocytes, and hence minor quantities of it are reported to be found in peripheral blood.

Similarly, the other two SCFAs, *i.e.* propionate and acetate, also play their role in maintaining colonic health but up to some extent. As compared to other SCFAs, acetate is produced in maximum amount nevertheless is quickly transported to the liver after being absorbed via the proximal

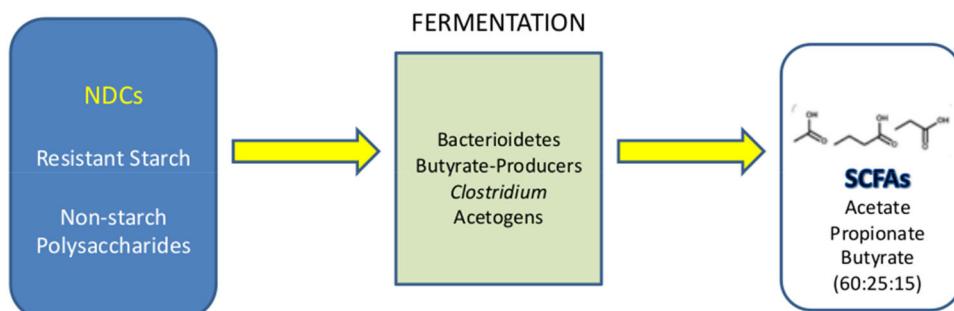


Figure 2. Production of short-chain fatty acids (SCFAs) from fermentation of non-digestible carbohydrates (NDCs).

colon, where it is utilized as a substrate in the synthesis of cholesterol (Boets et al. 2017; Wong et al. 2006). However, 90% of the third primary produced SCFAs, *i.e.* propionate, are also transported to the liver, acting as a substrate for other pathways like lipogenesis, gluconeogenesis, and protein synthesis. SCFAs not only act individually but moreover positively affects the production and functionality of each other. Additionally, reports have revealed high conversion frequency among these produced SCFAs, specifically from acetate to butyrate (Den Besten et al. 2013; Wolever et al. 1991; Wong et al. 2006). This review highlights the recent advances in applying SCFAs as important metabolites to treat various diseases and maintain colonic health.

Production and transport of SCFAs

The human intestinal lumen environment is defined by gut flora's metabolic activities (Hooper, Midtvedt, and Gordon 2002). NDCs are incompletely metabolized by the gut flora present in the anaerobic environment of lumen and results in the formation of SCFAs. Generally, Bacteroidetes acts as the critical fermenters in transforming the complex carbohydrates to organic acids, especially SCFAs and hydrogen. Further, some other fermenters like butyrate-producing bacteria and *Clostridium* species use these organic acids to liberate more SCFAs. Furthermore, acetogens utilize hydrogen as a source of energy and increase acetate content (Rey et al. 2010). Main SCFAs produced as a fermentation byproduct of resistant starches and fiber are butyrate, propionate, and acetate. These SCFAs are produced in a relatively high (70 to 140 mM) content in the proximal colon compared to their concentration in the distal colon and distal ileum, *i.e.* 20 to 70 mM & 20 to 40 mM, respectively (Wong et al. 2006). The molar proportion of acetate, propionate, and butyrate produced in the human colon is reported to be as 60:25:15, correspondingly. Variations in this molar ratio could be associated with several factors like genotype of the host, food, composition of gut microbiota, and fermentation site (Hamer et al. 2017; Tazoe et al. 2008).

NDCs are known to be the key substrates responsible for the production of SCFAs. Polysaccharides may be categorized into starch (amylose), starch-like (glycogen), and non-starch polysaccharides (NSPs). In the small intestines, the first two types of polysaccharides, *i.e.* starch and starch-like saccharides, are completely digestible and yield glucose molecules. On the other hand, polysaccharides that are partially/

incompletely digestible in the small intestines undergo fermentation in the presence of particular anaerobic colonic bacteria resulting in the production of SCFAs, heat, and gases. Such fermentable polysaccharides are known as dietary fibers or NSPs (non-starch polysaccharides) and RS (resistant starch). Degree of solubility further sub-categorizes dietary fibers as soluble or insoluble dietary fibers. As compared to soluble fibers, insoluble fibers produce more amount of SCFAs due to their rapid fermentability rate.

Nevertheless, resistant starch is the most dominant butyrogenic substrate as its fermentation results in abundant production of the butyrate (Englyst, Kingman, and Cummings 1992). Few other saccharide-based substrates for the production of SCFAs are fructooligosaccharides, galactooligosaccharides, and mannooligosaccharides (Pan et al. 2009). Despite this, a small amount of trace SCFAs (isovalerate & isobutyrate) is also formed from the catabolism of isoleucine, valine, and leucine. At the same time, lactate is also transformed into SCFAs (Macfarlane and Macfarlane 2003). Figure 2 depicts the production of SCFAs from the fermentation of NDCs.

Complex enzymatic pathways involved in yielding SCFAs from dietary fibers are active in various bacterial strains. The glycolytic pathway is known to be the predominant pathway in the production of the SCFAs in the bacteria. However, *Bifidobacteria* uses hexose monophosphate shunt to produce SCFAs (Cronin et al. 2011; Macfarlane and Macfarlane 2003). Likewise, the Wood-Ljungdahl pathway is the most effective pathway responsible for acetate's bacterial production (Fast and Papoutsakis 2012). Miller & Wolin (Miller and Wolin 1996) revealed that propionate is produced through the CO₂-fixation pathway, whereas acetyl-S coenzyme A condensation produces butyrate. Genus *bifidobacterium* uses fructose-6-phosphate phosphoketolase (F6PPK)-the pathway for the conversion of monosaccharides to SCFAs (Pokusaeva, Fitzgerald, and van Sinderen 2011). Pathways for acetate production are present among various bacteria groups, while those for butyrate and propionate production are substrate-specific and less expended. A mucin-degrading bacterium, *i.e.* *Akkermansia muciniphila* found in the human intestinal tract, is an actual specie for propionate production. Similarly, in the human colon, specie *Ruminococcus bromii* is known to ferment resistant starch and produce a significant butyrate amount. Secondly, other than the enzymatic requirements, protein transporters' expression is also defined as vital for the production of

SCFAs. In *Bifidobacterium longum* species, the occurrence of ATP-binding cassette (ABC) transporters are critical for the transportation of fructose for the production of acetate (Fukuda et al. 2011). In various bacterial groups, an additional mechanism, i.e. phosphoenolpyruvate (PEP)-dependent phosphotransferase system (PTS) is used for the uptake and transportation of carbohydrates to produce SCFA (Zoetendal et al. 2012).

As mentioned earlier, most of SCFAs are produced and used in the gut's locality; just a small quantity of acetate and propionate is taken up by the liver and are utilized in various other metabolic pathways. A small percentage of these SCFAs subsists in the unionized form in the gut and could straightly cross the epithelial barrier while the remaining major quantity of SCFAs are in ionized form, and specific transporters are required for their absorption. The monocarboxylate transporter (MCT)-1 and sodium-monocarboxylate transporter (SMCT)-1 are the two chief receptors involved in facilitating the active transport of SCFAs through the mucosa. Both these receptors are present on colonocytes, cecum, & small intestine, while MCT-1 and SMCT-1 are also expressed on lymphocytes, thyroid glands, and kidneys (Halestrap and Wilson 2012; Iwanaga et al. 2006).

Biological functionality of SCFAs

The main health effects ascribed with SCFA production are associated with the decrease in luminal pH, which further results in the inhibition of pathogenic microbes and elevates nutrient absorption (Macfarlane and Macfarlane 2012). Acetate production has been reported as a vital metabolite responsible for enhancing the capability of *Bifidobacterium* in inhibiting enteropathogens (Fukuda et al. 2011). Similarly, the absorption of butyrate by colonocytes significantly affects energy homeostasis (Wong et al. 2006). Additionally, the production of SCFAs also modulates the immune system functionality in host organisms. The SLC5A8 transporter is responsible for the uptake of SCFAs (e.g., propionate and butyrate) into immune cells, where they inhibit histone deacetylases' activity (HDAC). Immuno-modulating perspectives of these SCFAs may be due to the upregulation of FAS resulting in T-cell apoptosis (Singh et al. 2010; Zimmerman et al. 2012). A substantial amount of SCFAs produced by gut microbiota in maintaining intestinal immune system homeostasis is of great concern as butyrate modulate the expression of pro-inflammatory cytokines interleukin (IL)-12 and IL-23 in experimented dendritic cells (Berndt et al. 2012).

Multifarious mechanisms responsible for the biological significance of SCFAs on the mucosal immune system consist of regulating varied cellular pathways in dendritic, epithelial, and T-cells and the influence on the immunometabolism and epigenetic regulation of lymphocytes. Significantly, SCFAs effectively inhibits the activity of HDACs (histone deacetylases) and therefore attenuates autoimmune diseases and intestinal inflammation (Luu, Monning, and Visekruna 2020). SCFAs, specifically butyrate and propionate, have shown beneficial effects in curtailing

various metabolic ailments like diabetes, obesity and inflammatory bowel disease (IBD) via modification of TFs (transcription factors) and activation of specific GPCRs (G protein-coupled receptors) (Puertollano, Kolida, and Yaqoob 2014). Numerous studies have demonstrated the role of propionate and butyrate in the regulation of inflammation, production of gut hormones, and obesity, as they bind to G-protein coupled free fatty acid receptor (FFAR)-2 (GPR43) & 3 (GPR41), respectively present at epithelium sites (Layden et al. 2013; Xiong et al. 2004). The experimented mice deficient in FFAR2 & FFAR3 showed a reduction in glucagon-like peptide contents (GLP)-1 and glucose tolerance, revealing the importance of SCFAs in diabetes (Tolhurst et al. 2012). The binding of SCFA with FFAR-2 results in suppressing intestinal inflammation as this mechanism was not observed in FFAR-2 deficient mice (Maslowski et al. 2009). Conclusively, scientific evidence reveals the significance of SCFAs produced by gut microbiota as a vital regulator in hormone production, energy homeostasis, and inflammation (Figure 3).

Intestinal gut microflora helps boost gut epithelium's defensive mechanism by enhancing the production of antimicrobial peptides (AMPs) (Gallo and Hooper 2012). In the human colonic epithelial cell line, the gut microbiota has reported stimulating the AMPs production via SCFAs dependent induction of antimicrobial peptide LL-37 (Termén et al. 2008). Likewise, SCFAs elevated the expression of the peptide gene, increasing the host defense system. Further, the administration of exogenous SCFAs through feed-in chickens also showed reduced colonization of *Salmonella* in the cecum (Sunkara et al. 2011; Sunkara, Jiang, and Zhang 2012).

Virulence regulation of enteric pathogens by SCFAs

Free fatty acids, including short- and medium-chain fatty acids, have been shown to possess significant antimicrobial activity against a wide range of microorganisms and are being extensively used in the food, agriculture, and medicinal industry. For instance, propionate has found its applications as a potential antimicrobial food additive is routinely used as an antimicrobial additive in food (Arora, Sharma, and Frost 2011) whereas, the ability of butyrate to control *Salmonella* infections has also been reported through in vivo trials (Fernández-Rubio et al. 2009). Several mechanistic approaches have been associated with the antimicrobial activity of free fatty acids, including imbalanced nutrient uptake, irregular energy generation, disturbance of osmotic balance, and pH change (Figure 4). Moreover, a key benefit of using free fatty acids for inactivating microbial cells is their low concentration without imposing hazardous health impacts on the host cells (Dewulf et al. 2011). In this regard, Hong et al. (Hong et al. 2005) demonstrated that butyrate, formic acid, propionate, hexanoic acid, and acetate could exert momentous biostatic and biocidal effect on different oral microorganisms even at very low (μM) concentrations. Studies have also affirmed that hexanoic acid and propionate promote the expression of antimicrobial peptides in a host,

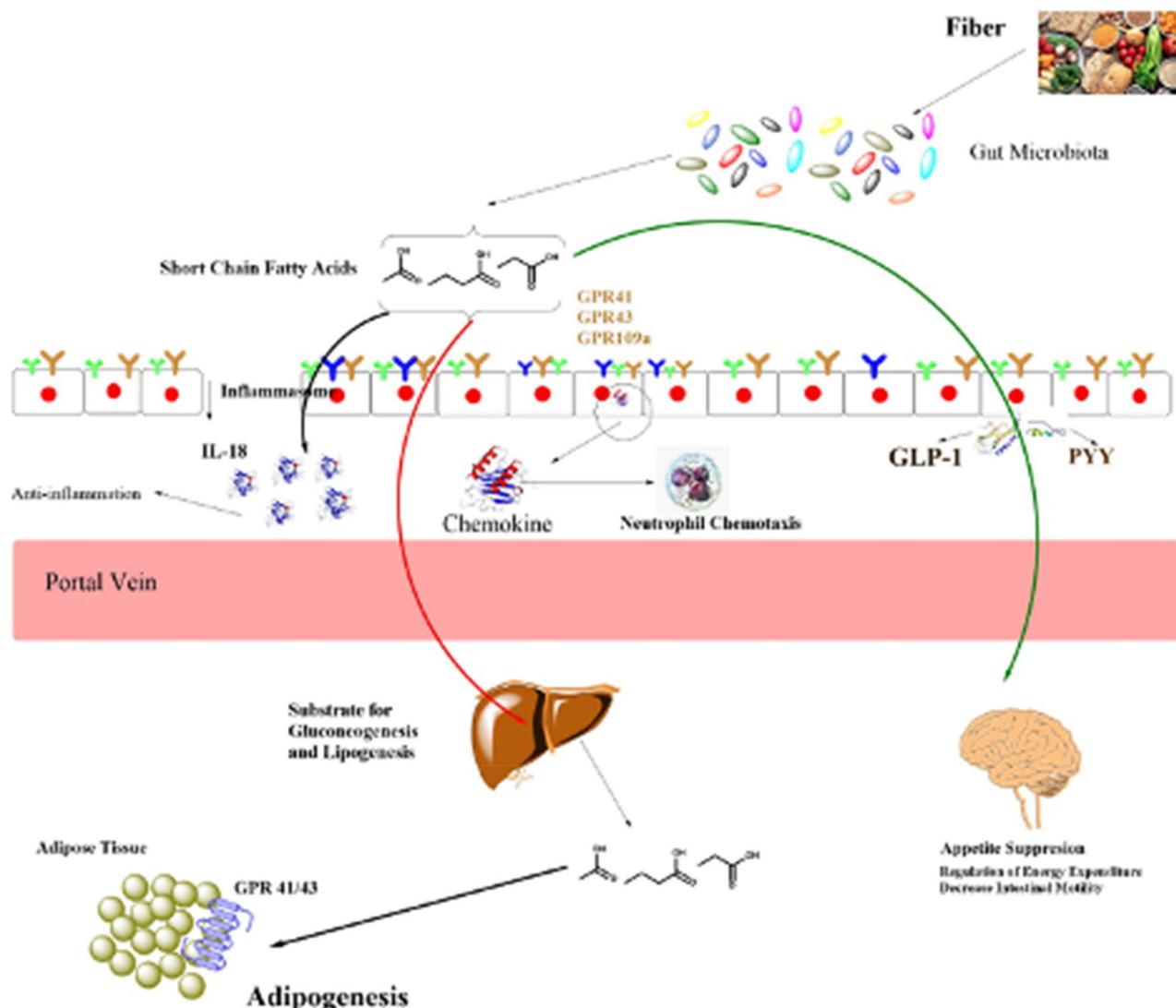


Figure 3. Scheme of the role of short-chain fatty acids (SCFAs) on energy metabolism (modified from Pekmez et al. 2019). Abbreviations: IL-18, interleukin-18; GLP-1, glucagon-like peptide-1; GPR g-protein coupled receptors; PYY, polypeptide YY.

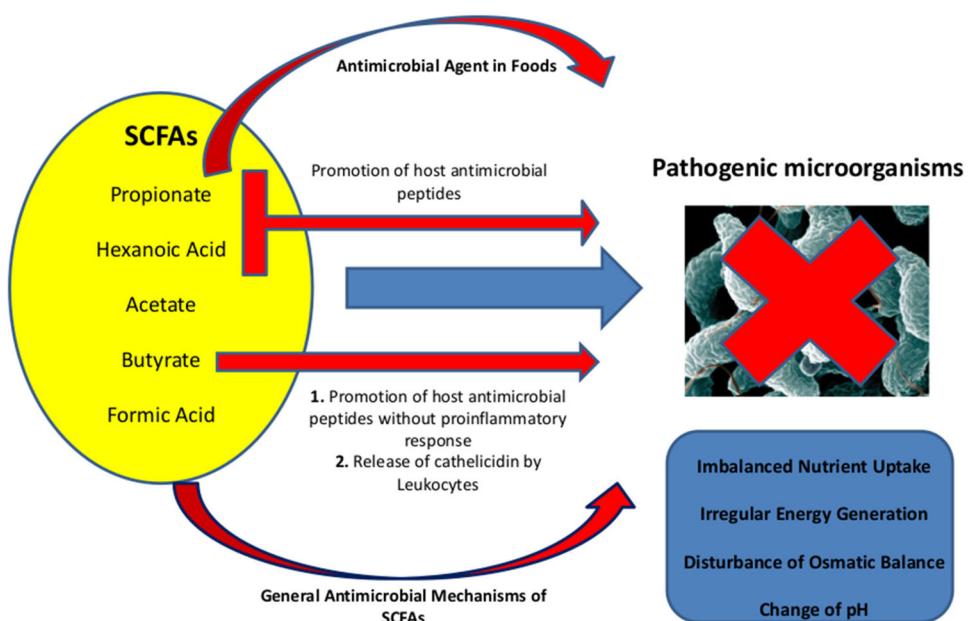


Figure 4. Mechanisms and factors influenced by SCFAs in the control of intestinal bacterial pathogens.

INHIBITION OF SALMONELLA TYPE III SECRETION SYSTEMS (T3SS)

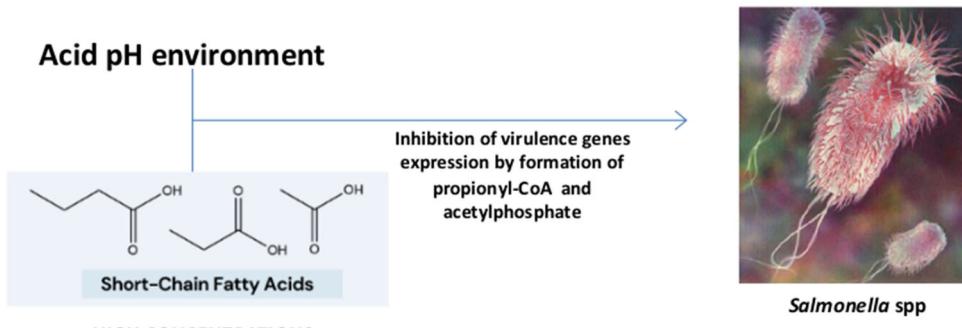


Figure 5. Influence of SCFAs and pH in the resistance decreasing of *Salmonella* spp.

which enhances their natural defence mechanism against microbial infections (Alva-Murillo, Ochoa-Zarzosa, and López-Meza 2012).

Similarly, oral administration of butyrate for treating *Salmonella* infection also boosts host peptides' defence system without triggering the proinflammatory response due to lower production of Interleukin 1 beta (IL-1 β) (Sunkara, Jiang, and Zhang 2012). Besides, butyrate treatment is also responsible for increasing the efficiency of cathelicidin through HDAC inhibitors by stimulating polymorphonuclear leukocytes' activity to enhance the release of cathelicidin (Kida, Shimizu, and Kuwano 2006). It has also been found through investigations that the antimicrobial activity of SCFAs is particular and maybe inert for some bacterial species but highly effective against some other microbial species (Alva-Murillo, Ochoa-Zarzosa, and López-Meza 2012). Consequently, SCFAs' production plays a considerable job in shaping the gut's microbial ecology; however, the detailed and specific effects of SCFAs on selecting bacterial species need further exploration.

Molecular response to SCFAs in pathogenic *Salmonella* species

According to a report published by the Centers for Disease Control and Prevention (CDC), USA *Salmonella* infection is considered among the most critical type of foodborne illnesses affecting around 1.35 million people annually in the United States alone (CDC and C. f. D. C. a. P 2020b). The most common serotypes (subspecies or serovar) of *Salmonella enterica* in this regard include *typhimurium*, *enteritis*, and *newport* account for about 60% of the total *Salmonella*-induced infections. *Salmonella* pathogenicity's primary mechanism is the injection of bacterial effector proteins in the cellular cytoplasm via Type III Secretion Systems (T3SS). This pathway can be blocked by administering SCFAs, which prevents gastrointestinal *Salmonella* infection (Galán 2001). Therefore, it is essential to understand the response of *Salmonella* toward SCFAs to unveil the key aspects which can help provide useful information to design proper strategies for the prevention and cure of this infection.

Molecular response to SCFAs has been widely reported in various investigations involved in the study of *Salmonella* pathogenesis (Figure 5). At lower levels of SCFAs, for instance, propionate, *Salmonella* can assimilate SCFAs and use them as a primary carbon source (Horswill and Escalante-Semerena 1999). However, higher concentrations of SCFAs along with a low pH environment provide potent inhibition against *Salmonella* growth (McHan and Shotts 1993; Van Immerseel et al. 2003) which is the main reason for using SCFAs as food and feed (poultry) preservatives to control the *Salmonella*-associated contamination (Wales, Allen, and Davies 2010).

Pathogenic *Salmonella* species adopt various active mechanistic responses for survival in an acidic environment with high levels of SCFAs, mainly by abolishing the accumulation of proton in the cytosol (Álvarez-Ordóñez et al. 2011). Additionally, SCFAs can regulate *Salmonella* virulence's gene expression in a species- and pH-specific manner, as evidenced through in vitro trials (Díaz and Ricke 2004; Gantois et al. 2006; Gong et al. 2009; Huang et al. 2008). For instance, the administration of SCFAs having two to six carbon atoms can induce *spvABCD* genes responsible for the virulence of *Salmonella dublin* (El-Gedaily, Paesold, and Krause 1997). Contrarily, individual supplementation of propionate or butyrate is reported to reduce the invasion genes expression in *S. typhimurium*. Moreover, higher levels of SCFAs in the colon are more effective in inhibiting *S. typhimurium*'s growth than ileal concentrations (Lawhon et al. 2002).

The comprehensive studies exploring the inhibitory mechanisms of SCFAs revealed that SCFAs are associated with propionyl-CoA formation (from propionate) and acetyl phosphate (from acetate), which regulate the virulence gene expression. The in vitro investigations on the variations in the expression of virulence genes under the influence of SCFAs using animal and tissue culture modeling have also explained the mechanisms of inhibitory action of SCFAs (Hung et al. 2013; Lawhon et al. 2002). In this perspective, Durant et al. (Durant et al. 1999) studied the inhibitory effect of butyrate, acetate, and propionate on *S. typhimurium* at different pH values and reported that cellular association of bacterial infection is highly dependent on pH. They

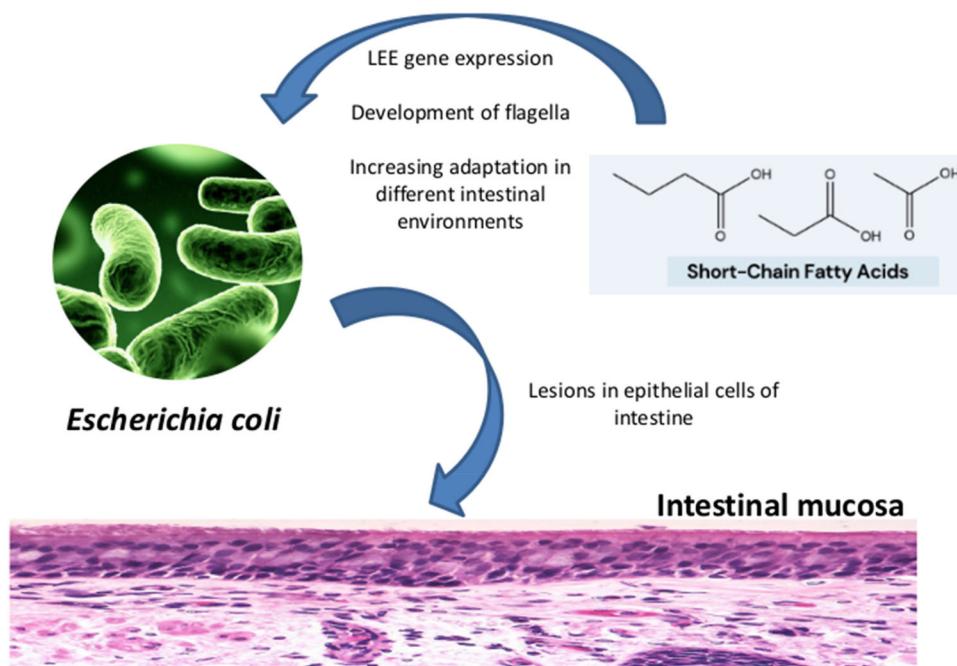


Figure 6. Involvement of SCFAs in the adaptation and virulence of *Escherichia coli* in the intestinal environment.

further explored that pH values of 6 and 7 were most effective in reducing the cellular association. In primary chicken cecal epithelial cells, it was reported that butyrate treatment reduced the invasion of *S. enteritis* in avian intestinal DIV-1 cell lines (Immerseel et al. 2004; Van Immerseel et al. 2003). Studies based on animal modeling also provide evidence regarding the beneficial effects of supplementing feed with SCFAs in reducing the invasion of *Salmonella* in chick (McHan and Shotts 1992) and pig ceca (Boyen et al. 2008). Altogether, these trials' findings revealed that subjects with adequate gut microbiota produced SCFAs, particularly propionate and butyrate, are less expected to be vulnerable to *Salmonella* infections.

Functionality of SCFAs in *Escherichia coli*-induced pathogenesis

Among various *Escherichia coli*, enterohemorrhagic *E. coli* (EHEC) is the leading cause of foodborne pathogenicity by eroding the lesions' epithelial cells present in the intestine through producing and releasing effector proteins into the host cytoplasm by T3SS (Wong et al. 2011) Figure 6. The infection is triggered due to the presence of several virulence determinants on the chromosomal locus for enterocyte effacement (LEE). Studies containing transcriptomic and protein assays have demonstrated that LEE gene expression in EHEC (Sakai strain) is induced primarily due to the higher intestinal concentrations of sodium butyrate but not sodium propionate and sodium acetate (Nakanishi et al. 2009). This elevated activity of EHEC is mainly due to leucine-responsive regulatory protein (Lrp) (Nakanishi et al. 2009), which is present in bacterial cells and involved in the metabolic response to the availability of different nutrients; (Calvo and Matthews 1994; Lango-Scholey et al. 2013; Newman and Lin 1995; Yokoyama et al. 2006). In contrast

to butyrate activity in promoting bacterial cells' adherence, all three main SCFAs are reported to provoke flagella development in EHEC by Lrp-dependent and independent pathways (Tobe, Nakanishi, and Sugimoto 2011). It has also been observed that intestinal colonization of EHEC results in the reduced uptake of butyrate in the human colonic Caco-2 cell lines (Borthakur et al. 2006). Another study demonstrated that elevated colonic levels of SCFAs support the capability of EHEC to traverse in different intestinal environments in response to different levels of SCFAs (Herold et al. 2009). Nevertheless, these findings' results do not support the significant ability of SCFAs in mitigating the intestinal attachment, colonization, and load of EHEC (Cobbolt and Desmarchelier 2004). Therefore, it is direly needed to investigate the efficacy of SCFAs in reducing EHEC pathogenesis through in vivo studies to elucidate better complex mechanisms involved in the functionality of SCFAs.

Protective effect of intestinal SCFAs against *Listeria monocytogenes* infections

Listeria monocytogenes is a potent contaminant in fermented dairy products and foods preserved using organic acids because of its ability to subsist and cultivate under acid conditions. However, the bacterium must resist the high acid stress in the stomach and the presence of SCFAs in the intestine for proper attachment, colonization, and induction of pathogenesis after ingestion (Figure 7). Therefore, a proper understanding of the response of *L. monocytogenes* is vital for a thoughtful investigation of bacterial pathogenicity and food safety. Studies have proposed that prior exposure of acids from food is responsible for enhancing the survival rate of *L. monocytogenes* in acid stress conditions (Davis, Coote, and O'Byrne 1996; Kroll and Patchett 1992;

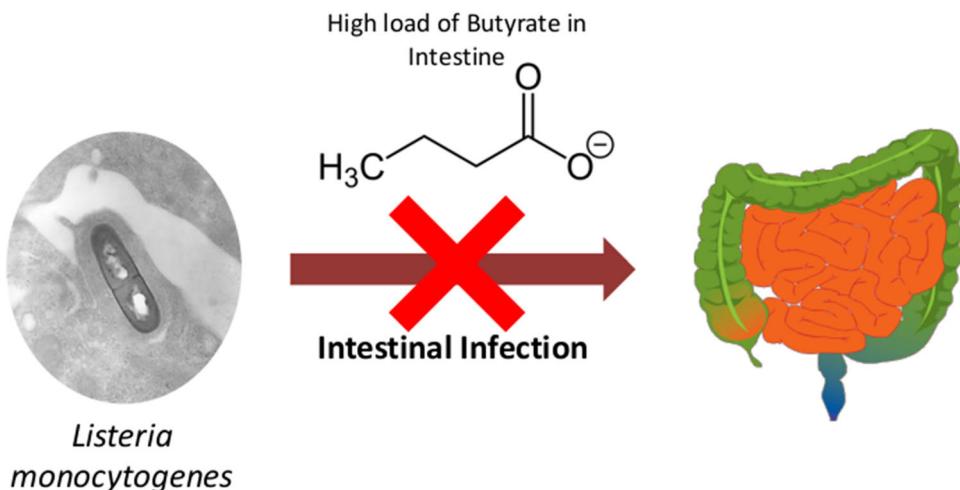


Figure 7. High intestinal concentration of butyrate controls infections caused by *L. monocytogenes*.

O'Driscoll, Gahan, and Hill 1996). This behavior, called acid tolerance response (ATR) (Cotter and Hill 2003; Ryan, Hill, and Gahan 2008), comprehends three primary adaptations of bacterial cells in response to the declined levels of intracellular pH (Shabala et al. 2006). These adaptations include the glutamate decarboxylase system (Cotter, Gahan, and Hill 2001; Cotter et al. 2005), F1F0 ATPase (Bowman et al. 2010; Bowman et al. 2012), and arginine-agmatine deiminase system (Ryan, Hill, and Gahan 2008). In addition to enhancing the survival rate of *L. monocytogenes* under acidic stress, ATR also plays an important role in fostering the virulence of *L. monocytogenes* (Conte et al. 2000; Conte et al. 2002; Marron et al. 1997).

Studies focusing on the effect of SCFAs' administration on the intestinal load of *L. monocytogenes* explain that higher concentrations of butyrate are strongly linked with reducing the pathogenicity of *L. monocytogenes* (Sun et al. 2012), supporting the protective function of SCFAs against *L. monocytogenes* infections. Although these findings are unable to explain the mechanisms involved in the reduced colonization of *L. monocytogenes* due to higher intestinal levels of SCFAs, thus, require further comprehensive work for mechanistic understanding about the effect of SCFAs on the pathogenicity of *L. monocytogenes* and regulation of gene expression.

SCFAs in protecting *Campylobacter jejuni* infections

Campylobacter jejuni is one of the major foodborne pathogens responsible for inducing diarrheal disease in humans, with an infection rate of about 1.5 million people annually, as reported by The CDC, USA (CDC and C. f. D. C. a. P 2020a). Contaminated chickens have pondered the primary cause of *C. jejuni* exposure. Therefore several studies have been conducted to explore various strategies for minimizing the *C. jejuni* infections (Hermans et al. 2011), including investigations focused on studying the impact of administering SCFAs in the animal feed on the intestinal attachment and colonization of *C. jejuni* (Heres et al. 2004; Heres et al. 2003; Van Deun et al. 2008). However, these studies

do not provide strong evidence regarding the protective effect of SCFAs on *C. jejuni* colonization. Additionally, studies evaluating the virulence response of *C. jejuni* to SCFA pretreatment through tissue culture modeling stated that *C. jejuni* invasion to human colonic epithelium-derived Caco-2 cells is not compromised after SCFAs treatment. However, pretreatment of Caco-2 cells resulted in a significant reduction in the subsequent invasion of *C. jejuni* (Van Deun et al. 2008). It can be evident from the findings that SCFAs might not be involved in altering the regulation of virulence genes in *C. jejuni* but can protect the host against *C. jejuni* pathogenicity (Figure 8).

In another investigation, *C. jejuni* cells were exposed to the mixture of SCFAs (butyrate, acetate, and propionate) in the intestinal tract of chicks to elucidate the combined impact of SCFAs in stimulating the acetogenesis-dependent gene expression in *C. jejuni* *Apta ackA* mutant (CDM). Purposely, CDM was supplemented with a mixture of SCFAs containing 5 mM butyrate, 7.5 mM and 30 mM acetate, followed by studying *ggt*, *peb1c* and *Cjj0683* gene expressions. Results stated that SCFAs incorporation did not alter *Cjj0683* and *ggt* gene expressions, but a slight reduction was observed in the expression of *peb1c*. These findings support the potential of SCFAs in alleviating *C. jejuni* pathogenesis by regulating gene expressions, but detailed work is needed to explicate further the exact mechanisms responsible for this functionality of SFAs (Luethy et al. 2017).

SCFAs against *shigella* infection

Shigella is considered another essential model of the enteric pathogenic bacterium, widely investigated to probe the host-pathogen interactions. Islam et al. (Islam et al. 2001) postulated that *Shigella* infection is associated with causing a considerable downrigger in catheter production, which is an integral part of the innate defence system in tissue culture models and human rectal mucosal biopsies (Van Deun et al. 2008). Studies have revealed that chances of *Shigella* infection can be reduced by oral administration or bolus infusion of different SCFAs in the colon, particularly butyrate.

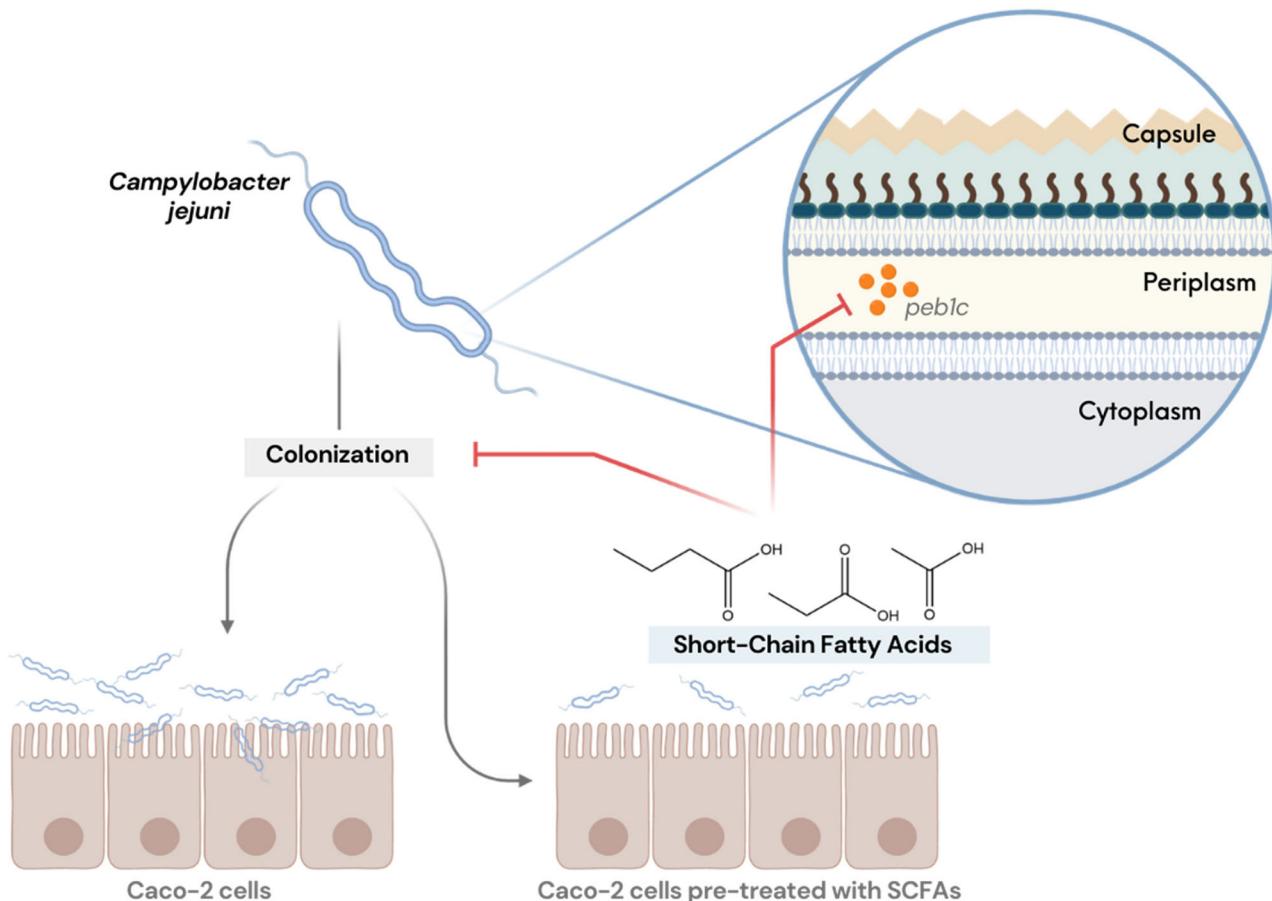


Figure 8. Probable protection mechanism against *C. jejuni* through the administration of SCFAs.

Evidence gathered through rabbit modeling has validated that both methods are useful in significantly improving clinical manifestations (Rabbani et al. 1999; Raqib et al. 2006). The potential mechanism of SCFAs' functionality in reducing *Shigella*-induced pathogenicity is chiefly centered on the upregulation of cathelicidin, which helps eliminate *Shigella* (Figure 9). Later on, human clinical trials were conducted in which butyrate-containing enemas were given to the patients suffering from *Shigella* infections, and the results showed an augmented cathelicidin expression compared to the patients receiving the placebo control (Raqib et al. 2012). However, further exploration is needed to define the direct mechanisms involved in protecting SCFAs on *Shigella* pathogenicity.

Anti-inflammatory and anti-tumorigenic roles of SCFAs

Anti-inflammatory perspectives of SCFAs are well documented as they modulate the release of cytokines and reactive oxygen species (ROS) (Figure 10). In human monocytes, SCFAs possess anti-inflammatory potential. For instance, butyrate inhibits the production of pro-inflammatory cytokines (e.g., IL-12, IL-1 β & tumor necrosis factor (TNF) α), nitric oxide (NO; an inflammatory stimulus), and nuclear factor (NF- κ B (a pro-inflammatory transcription factor), while, upregulates the production of anti-inflammatory cytokine IL-10 (Ni et al. 2010; Säemann et al. 2000; Segain et al. 2000). All three main SCFAs, i.e. butyrate, propionate, and

acetate, when administrated at the concentration of 30 mM, significantly reduced lipopolysaccharide (LPS)-induced TNF α release without disturbing the release of IL-8 proteins. In Colo320DM cells, butyrate, propionate, and acetate suppressed the activity of NF- κ B. Further, a significant decrease in the release of IL-6 from organ cultures was noticed in the case of all the examined SCFAs (Tedelind et al. 2007). SCFAs modulate inflammatory and immune responses through activating FFAR2, FFAR3, and GPR109A and inhibiting the activity of HDACs (Li et al. 2018a). Butyrate inhibits the activity of HDAC and modulates the production of pro-inflammatory cytokines; therefore is helpful against atherosclerosis and vascular inflammation (Hoffman et al. 2017). According to another investigation, in LPS-activated mononuclear cells and neutrophils, application of both propionate and butyrate inhibited the activity of NF- κ B and decreased the production of TNF α mainly due to suppression of HDACs. Moreover, both these SCFAs induced apoptosis via caspase-8 & 9 pathways (Aoyama, Kotani, and Usami 2010).

Inflammatory Bowel Diseases (IBD) occurs due to complicated chemistry among various factors like immunological, genetics, microbiological, and environmental. Dysbiosis of gut microbiota is known as one cause linking with IBD. Compared to a healthy person, patients suffering from IBD have decreased microbiota content in their feces and mucosa. These gut microbiotas are responsible for the fermentation of fibrous material and the production of

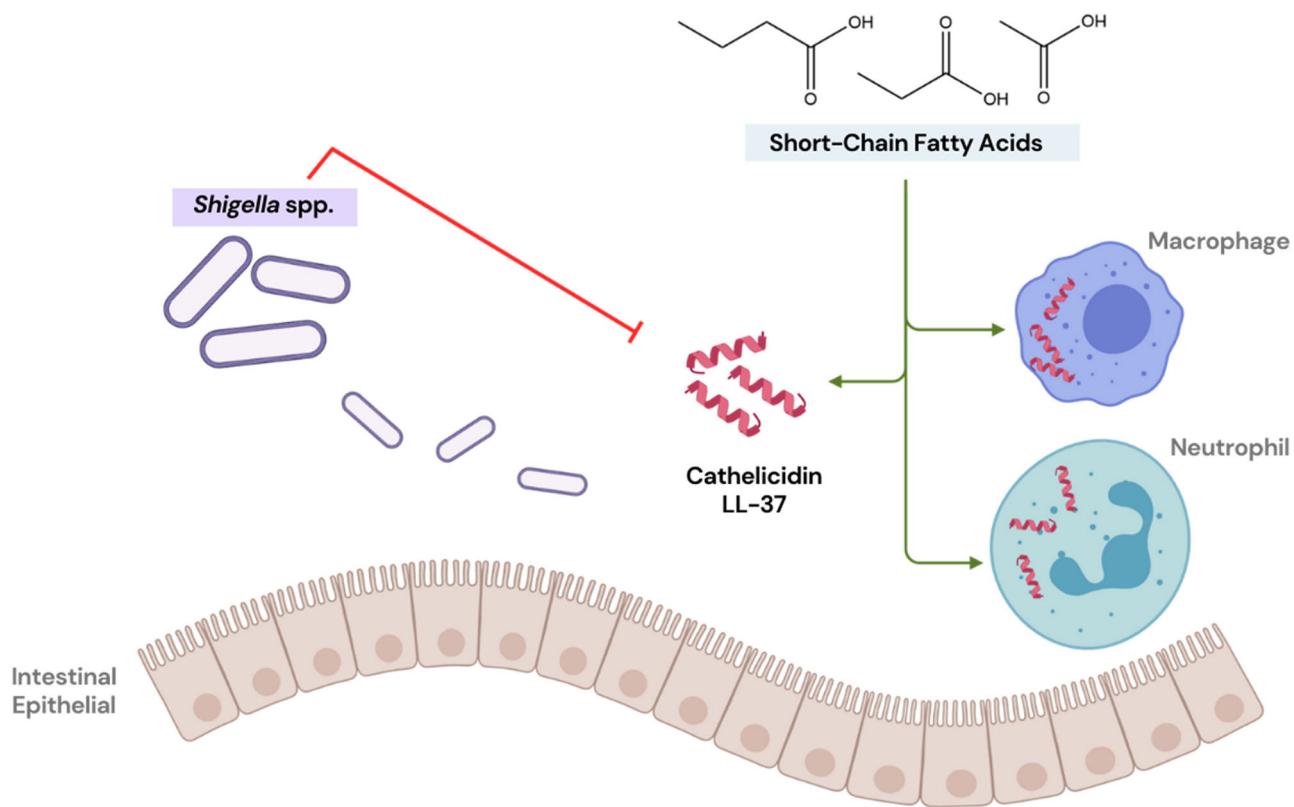


Figure 9. Regulation of cathelicidin levels promoted by the administration of SCFAs, in order to induce the cells of the host immune system to fight infection caused by *Shigella*.

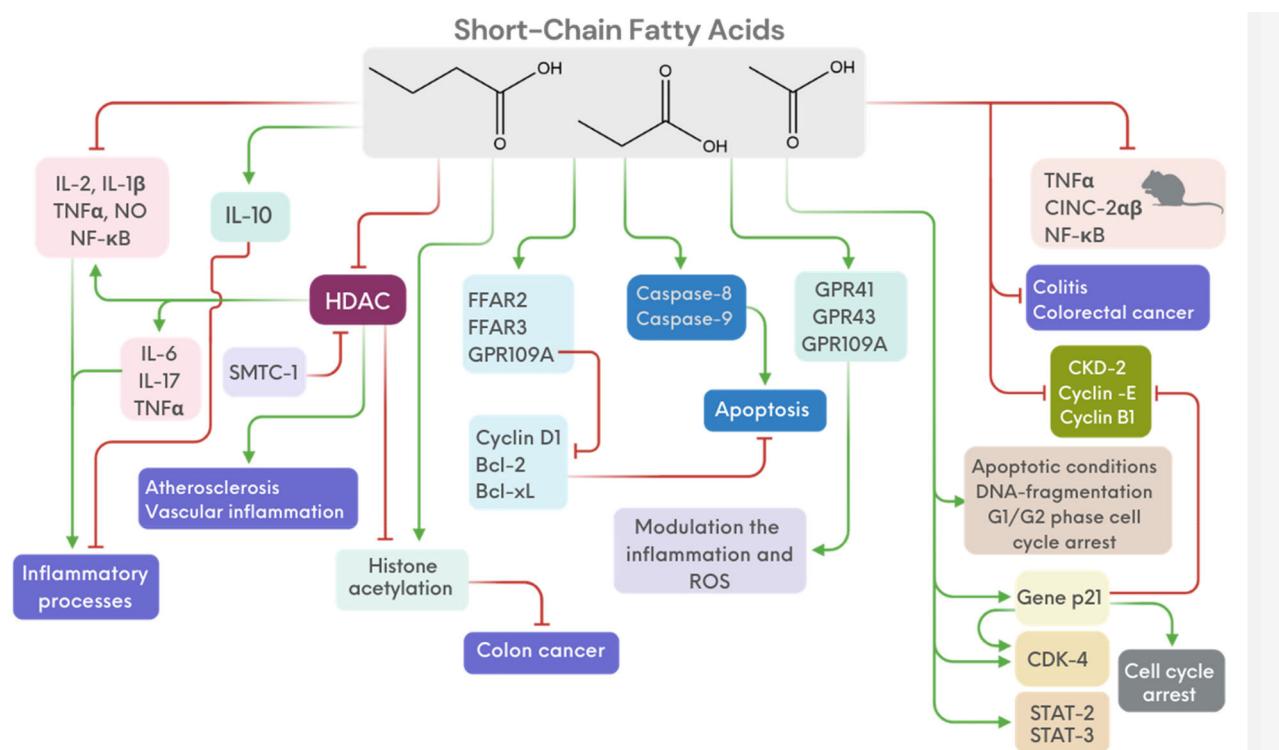


Figure 10. Chain of anti-inflammatory and anti-tumor mechanisms promoted by the presence of SCFAs.

SCFAs. Various studies have indicated a decreased concentration of SCFAs in IBD patients. To stimulate signaling cascades controlling the immune system functionalities, SCFAs signals via GPR41, GPR43, & GPR109A present at the

surface of the cell (Parada Venegas et al. 2019). Besides just being a source of energy for gut epithelial cells, SCFAs also possess a potential for the novel drug industry. Vinolo et al. (Vinolo et al. 2009) examined the potential of butyrate,

acetate, and propionate on TNF α production and cytokine-induced neutrophil chemoattractant (CINC)-2 $\alpha\beta$ in rat neutrophils. In LPS-stimulated neutrophils, butyrate and propionate reduced the production of NO, TNF α , and CINC-2 $\alpha\beta$. They further reported inhibition in the activity of HDAC and activation of NF- κ B hence authenticating the role of these SCFAs for the treatment of inflammation (Vinolo et al. 2011). SCFAs have modulating effect on inflammatory and immune responses through the inhibitory activity of HDACs and activation of GPR109A (G-protein-coupled receptor 109 A), FFA2 (free fatty acid receptor type 2) and FFA3 (free fatty acid receptors type 3) (Li et al. 2018b). In mature immuno-cytes and enterocytes, SCFAs have shown anti-inflammatory properties while less data are available that highlights their potential in immature intestines. Results of exposure of SCFAs to fetal mouse intestine, human fetal cell-line and fetal intestinal organoids have revealed anti-inflammatory potentials (Zheng et al. 2020).

Butyrate is produced in the colon through anaerobic fermentation and possesses shielding effects in colon carcinogenesis. In human colon carcinoma cells, propionate and valerate resulted in differentiation and cell arrest due to histone hyper-acetylation, but this magnitude was less compared to butyrate. SCFAs induced cell arrest by down-regulating the expression of cyclin B1 (CB1) and up-regulating p21 cell cycle inhibitors (Hinnebusch et al. 2002). The rate of propagation was not altered by SCFAs in p21 deleted HCT-116 colon cancer cells. Thus, it was suggested that the anti-proliferative and apoptotic potential of SCFAs are related to the extent to which they induce histone hyperacetylation, and SCFA induced cell cycle arrest involves gene p21 (Hinnebusch et al. 2002). Despite the inhibition of neutrophil functionality, butyrate has reported suppressing IL-2 and lymphocytic proliferation (Cavagliari et al. 2003). As mentioned earlier, SCFAs act as anti-inflammatory mediators by suppressing pro-inflammatory cytokines from neutrophils and macrophages. The binding of SCFAs with GPR43 (FFAR2) affects the inflammatory responses as concluded from experimentation on the Gpr43^{-/-} mice model. In GPR43 deficient mice, inflammation conditions were worsened in asthmatic, arthritic, and colitis models.

Similarly, the dysfunctionality of inflammatory responses was noticed in germ-free mice (mice deficient in gut microbiota). Therefore, the binding of SCFAs with the GPR43 receptor possibly responsible for a linkage among food, metabolism by gut microbiota, and immune & inflammatory responses (Maslowski et al. 2009). Ingestion of a diet rich in dietary fiber has demonstrated beneficial effects in patients who have colitis. The anti-tumorigenic effect of SCFAs in colitis-linked colorectal cancer was examined in a BALB/c mice model in which induction was achieved with DSS (dextran sodium sulfate) and AOM (azoxymethane). A mixture of SCFAs (acetate: 67.5 mM; butyrate: 40 mM; propionate: 25.9 mM) was subjected to experimented mice via drinking water during the whole course of the study. In AOM/DSS induced colitis-colorectal cancer mice model, a mixture of SCFAs resulted in a reduction of tumor size, tumor incidence, and inflammation by inhibiting pro-inflammatory

action cytokines TNF α , IL-6, and IL-17. Conclusively, administration of SCFAs decreased the biomarkers of cell proliferation, inflammation, and development of tumor cells in experimented with colitis-associated colorectal cancer mice model (Tian et al. 2018).

In colon cancer HTC116 cell lines, treatment of butyrate resulted in the induction of apoptotic conditions, DNA-fragmentation, and increased G1/G2 phase cell cycle arrest (Zhang et al. 2015; Zheng et al. 2017). SCFA-butyrate possesses anticancer perspectives as it enhances expression of p21 and histone deacetylation in both NCM460 (normal colon cell line) and HCT116 while inhibited the expression of p-ERK1/2 in HCT116 cells (Zheng et al. 2019). Butyrate application on human liver cancer HCC-T cells upregulated the cyclin-dependent kinase (CKD)-4, signal transducer, and activator of transcription (STAT)-2 & STAT-3, down-regulated the cyclin-E & CKD-2. In cancer cells, butyrate reduced the malignant phenotype due to HDAC inhibition (Nakamura et al. 2001; Wakabayashi and Kratschmer 2005). In cancer cells, GPR109A expression is silenced due to DNA methylation and is re-expressed in the presence of nicotinate and butyrate. Expression of GPR109A results in apoptosis by down-regulating cyclin-D1, antiapoptotic B-cell lymphoma (Bcl)-2 and Bcl-extra-large (Bcl-xL) proteins, and upregulating death receptor pathway. Furthermore, butyrate inhibits the activation of NF- κ B in both normal colon cells and cancer colon cells (Thangaraju et al. 2009). Activation of SMCT-1, a butyrate transporter, is important for anti-tumorigenic functionality as its expression is down-regulated in colon cancer cells (Miyauchi et al. 2004). SMCT-1 transports butyrate in colon cells hence preventing the development of cancer phenotype via HDAC inhibitory action. Outcomes of various studies have revealed that diet comprising of cereals and whole-grain is linked with a decreased possibility of colorectal cancer, therefore, highlighting the anticancer role of SCFAs (Aune et al. 2011).

SCFAs and neurological disorders

It is necessary to synthesize new proteins to ensure long-lasting changes in learning and synaptic plasticity. For this purpose, long term memory progression and learning are developed through elevated histone acetylation enhanced via HDAC inhibitors (Casellas et al. 2007; Gibson et al. 2004; Hallert et al. 2003; Swennen, Courtin, and Delcour 2006). HDAC inhibiting characteristics associated with SCFAs have led scientists to conduct various animal studies, specifically focusing on utilizing butyrate in elevating histone acetylation in the brain throughout the memory formation phase. Outcomes of several such studies have proposed SCFAs as a potent memory and learning modulator due to their HDAC inhibitory action (Looijer-Van Langen and Dieleman 2009; Rasmussen and Hamaker 2017). Numerous studies have revealed that during various brain-related diseases, gut microbiota, and metabolome changes (Ganjali-Arjenaki and Rafieian-Kopaei 2018; Hill et al. 2014; Sasaki et al. 2018; Wéra, Lancellotti, and Oury 2016; Zhang et al. 2015). In Autism Spectrum Disorder (ASD), an imbalance of the

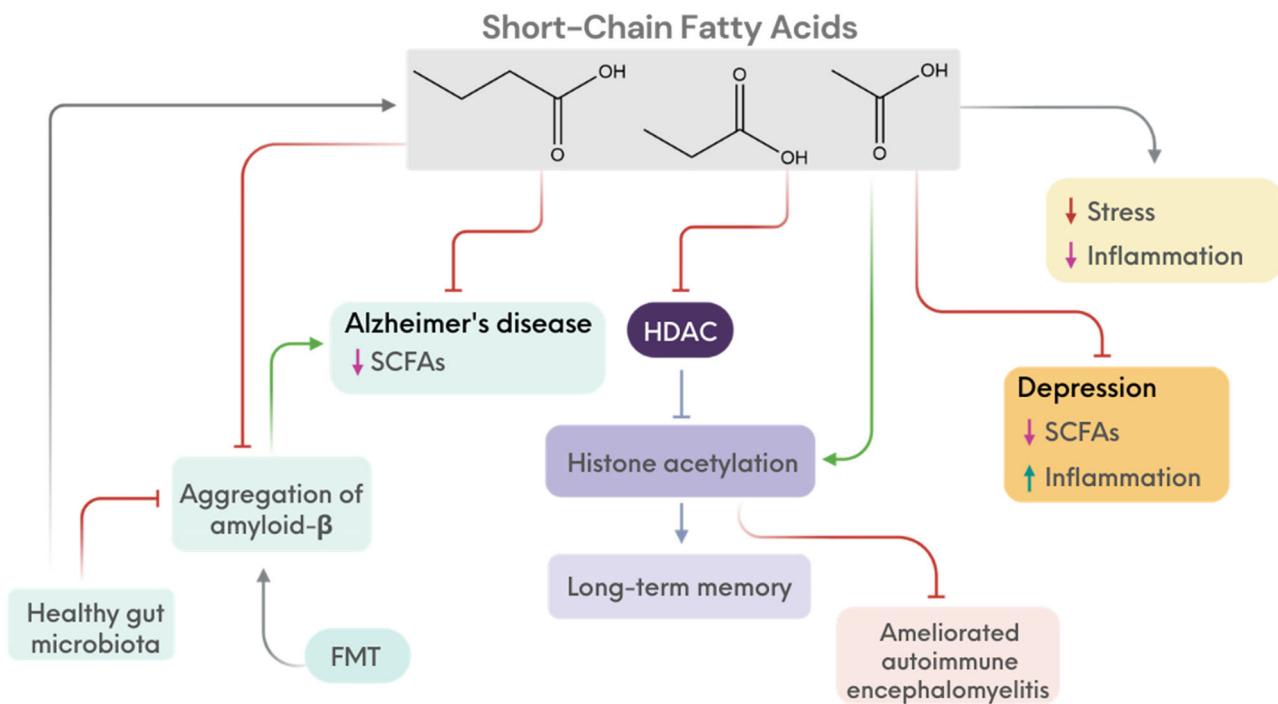


Figure 11. Factors regulated by SCFAs involved in the pathogenesis of neurodegenerative disorders.

composition of gut microbiota is existing. Sufficient evidence supporting this view is available from different animal investigations and clinical researches (Joossens et al. 2011). Nevertheless, the effect of SCFAs on ASD remains debatable. Wang et al. (Wang et al. 2012) while comparing with control subjects (111 mM kg^{-1}), reported elevated (136 mM kg^{-1}) concentration of total SCFAs in the feces of children who have ASD. Further, levels of butyrate and acetate were also increased in children with ASD compared to control children. Outcomes of this study could conclude that the process of fermentation and its byproducts (SCFAs) produced in the intestines could change in children having ASD as compared to normal children.

Depression is a mood-related disorder that impairs quality of life and results in social problems (Delgado-Vargas, Jiménez, and Paredes-López 2000). It is reported that patients suffering from depression have increased content of inflammatory biomarkers, and levels of pro-inflammatory cytokines are physio-pathologically important in this condition (Miller and Raison 2016). The concentration of SCFAs has also been lower in the naturally occurring non-human primate depression model (Deng et al. 2019). In agreement with these outcomes, a significant association was observed between the fecal content of SCFAs in patients having depression (Szczesniak et al. 2016). Further, Skonieczna-Żydecka et al. (Skonieczna-Żydecka et al. 2018) suggested a decreased concentration of SCFA in the feces of patients suffering from depression. As the potential of butyrate, the anti-depressant has been reported in various studies as it reverses behavioral changes (cognitive deficiencies & anhedonia) in animal models (Burokas et al. 2017; Sun and Buys 2016). Hence, the anti-inflammatory characteristics of SCFAs may help reduce the inflammatory biomarkers during the depression. Various scientific research has

demonstrated the potential of SCFA in reversing abnormal sociability while decreasing stress induced release of corticosterone (van de Wouw et al. 2018).

Various studies have revealed that SCFAs could modulate neuropathological processes occurring during Alzheimer's disease (AD) (Ho et al. 2018; Walsh et al. 2015; Zhang et al. 2017). AD pathology is quite complicated, and effective treatments against this disease are still deficient, so scientists focus on a diet-based regimen as an alternative strategy (Frozza, Lourenco, and De Felice 2018). Given the above-stated scenario, numerous studies have shown the relationship among healthy gut microbiota on halting AD and the association of dysbiosis and disease propagation (Cryan and Dinan 2012; Hill et al. 2014). Purposely, Zhang et al. (2017) reported a reduction in the concentration of SCFAs in an AD mouse model. Gut microbiota might help protect against AD, as SCFAs generated by this microbiota help inhibit the aggregation of amyloid- β (A β) (Ho et al. 2018). Fecal microbiota transplantation (FMT) is known as a powerful method for alleviation of AD. This hypothesis is supported by Sun et al. (Sun et al. 2019), who proposed that in APP/PS1 Tg (transgenic) mouse model treated with FMT reduced the aggregation of A β and reversed the cognitive impairments. They also noticed that FMT treatment in the Tg mouse model reduced cyclooxygenase concentration (COX)-2 and CD11b. Reversal of alterations in gut microbiota and their metabolites SCFAs may be the reason for this beneficial effect (Sun et al. 2019). The various factors regulated by SCFAs involved in the pathogenesis of neurodegenerative disorders is explained in Figure 11.

Multiple sclerosis is an auto-immune neurological disorder in which disproportion occurs among pro-inflammatory and anti-inflammatory cells that may be influenced by the composition of gut microbiota and its metabolites

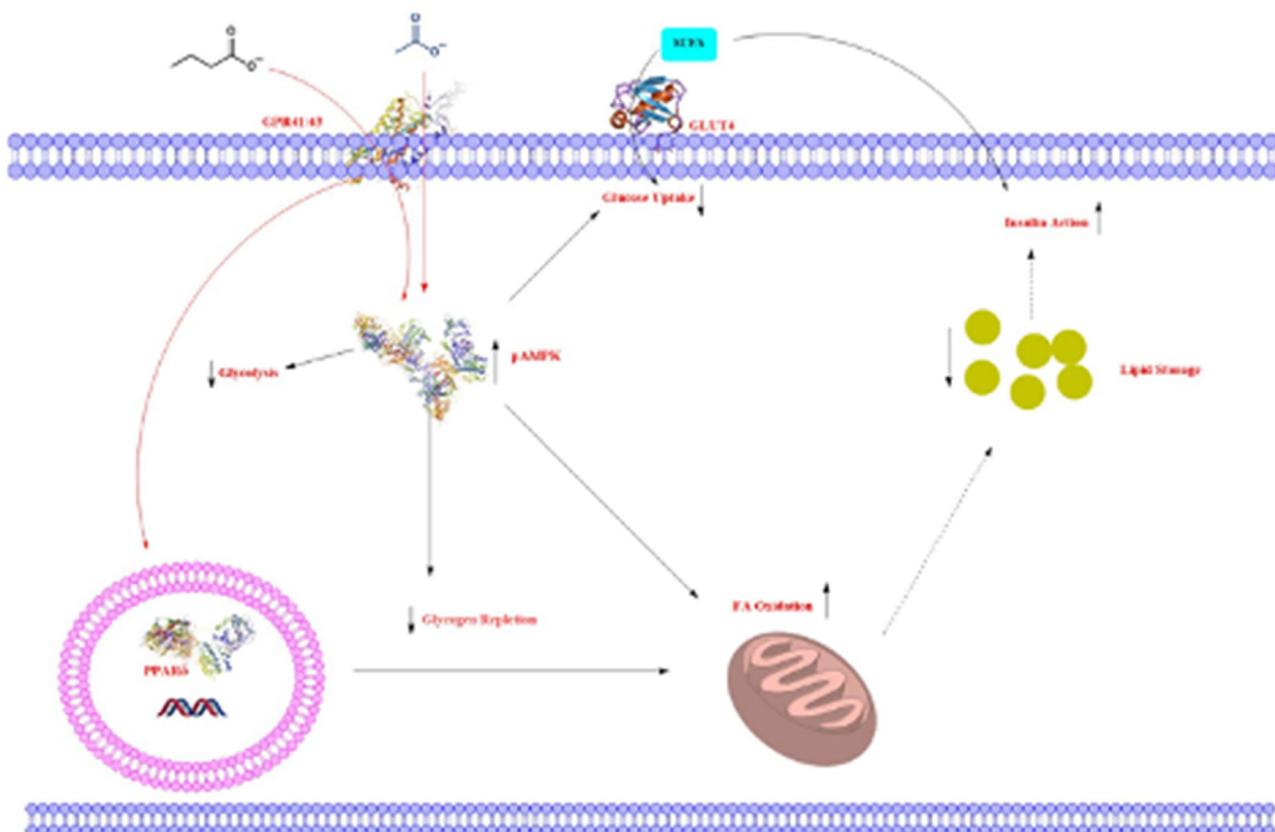


Figure 12. Schematic of SCFAs affection on diabetes and Obesity metabolic pathways. Abbreviations: SCFA, short chain fatty acids; GPR 41/43, g-protein coupled receptors 41 and 43; GLUT4, glucose transporter type 4.

SCFAs. This condition could worsen during dysbiosis (Jangi et al. 2016; Stanisavljević et al. 2019). SCFAs have the potential to induce Treg (T-regulatory) cells via inhibiting p38 & JNK1 pathways and ameliorated autoimmune encephalomyelitis (EAE) (Haghikia et al. 2015). Supplementation of acetate resulted in the elevation of acetyl-CoA metabolism leading to histone acetylation & preservation of lipid concentration in the spinal cord and therefore prevented the onset of autoimmune EAE (Chevalier and Rosenberger 2017). Moreover, butyrate treatment suppressed demyelination and increased remyelination by oligodendrocyte differentiation (Chen et al. 2019).

SCFAs and other metabolic ailments

Metabolic ailments comprise various clinical indicators such as diabetes, obesity, and cardiovascular diseases. These syndromes are thought to occur due to various factors like genetics, environmental factors, diet, and host lifestyle (Marette and Jobin 2015). Data from various studies have shown the possible connection between gut microbiota and metabolic ailments (e.g., obesity & type-2 diabetes). As compared to control subjects, the literature demonstrates alteration in gut microbiota composition in obese and type-2 diabetic animal models (Larsen et al. 2010; Sanna et al. 2019). An association between SCFAs production and metabolic syndromes has been established in a study conducted by Sanna et al. (Sanna et al. 2019), and suggested that elevation in the production of SCFA butyrate by gut microbiota may be linked

to augmented insulin response. Moreover, impairment in the production of SCFA propionate could be associated with more risk of type-2 diabetes. Likewise, outcomes of numerous studies have shown that ingested dietary fiber is associated with more production of SCFAs and therefore minimizes the risk of various metabolic syndromes. This may be due to gut microbiota's altered composition resulting in elevated SCFAs production (Kaczmarczyk, Miller, and Freund 2012).

Around the globe, the number of people suffering from obesity and type-2 diabetes is increasing at an alarming rate daily. The main two factors associated with these metabolic syndromes are unhealthy eating practices and a sedentary lifestyle. Compelling evidence has highlighted the importance of gut microbiota in minimizing the risk of these ailments. Role of gut microbiota and its metabolites, *i.e.* SCFAs in regulation pathways like signaling of insulin and production of hormone incretins (GLP-1 & GIP), results in reduced blood glucose levels (Baothman et al. 2016). Decreased gut production of SCFAs may also be linked with dysbiosis in type-1 diabetes (Jayasimhan and Mariño 2019). Consumption of dietary fibers through diet is linked to various health-promoting benefits such as ameliorate insulin resistance and obesity. This may be associated with the elevated production of SCFAs (butyrate, acetate, & propionate) formed due to fiber's fermentation in the colon.

Further, supplementation of SCFAs butyrate has also resulted in the prevention of fat-rich diet-induced obesity and insulin resistance (McNabney and Henagan 2017).

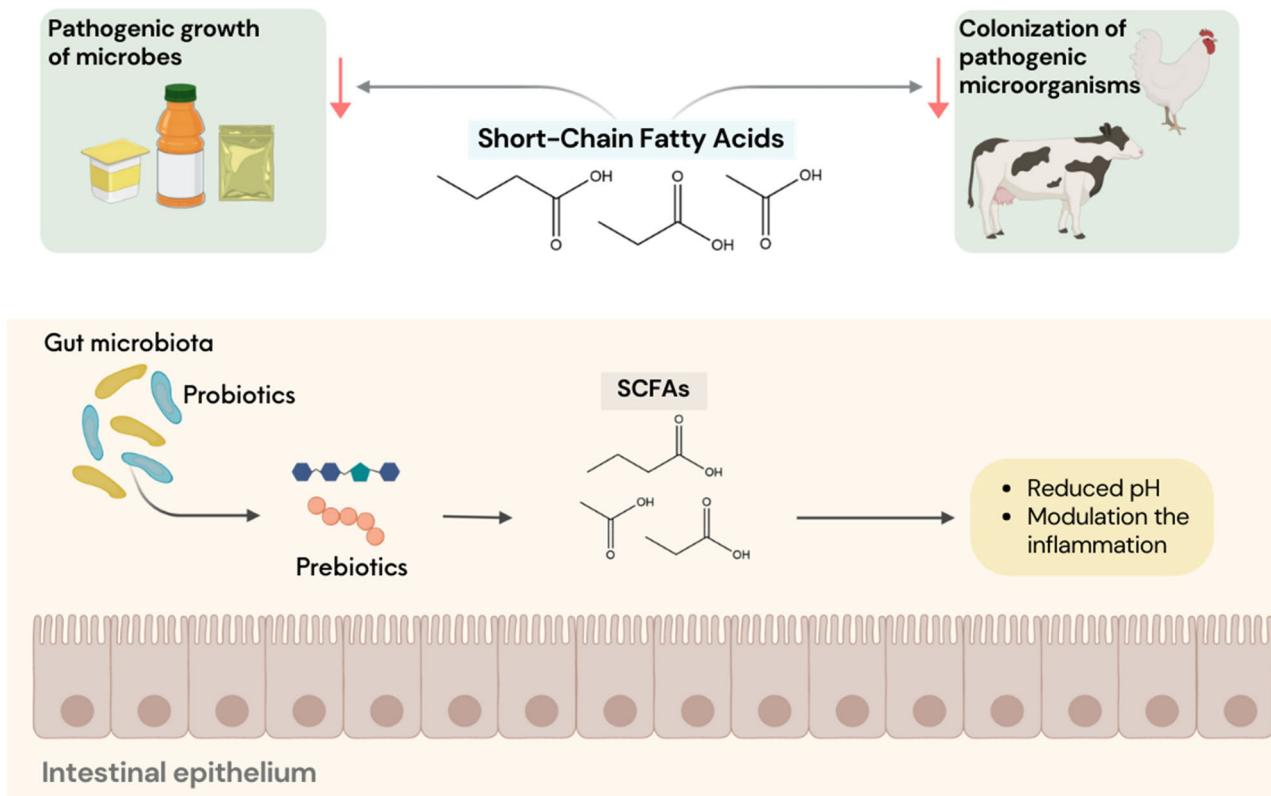


Figure 13. Applicability of SCFAs in the food industry, reducing the possibility of infection by pathogenic bacteria.

SCFAs, such as acetate and butyrate, helped protect against fat diet-induced obesity, whereas propionate was reported to minimize food intake. The proposed mechanism suggests that SCFAs might have regulated gut hormones' productions through FFAR2 & FFAR3 endogenic receptors (Lin et al. 2012). Stimulation of these receptors suppressed the orexiogenic neurons' activity responsible for expressing neuropeptide-Y in the hypothalamus, and further modulated the mediation by ghrelin receptor, therefore, contributed to controlling appetite (Li et al. 2018a; Torres-Fuentes et al., 2019). Animal studies have shown that ingestion of prebiotics increases the production of SCFAs, especially butyrate, and results in health modulating characteristics that are linked to increased GLP-1 contents and elevated expression of pro-opiomelanocortin in the hypothalamus (Ahmadi et al. 2019; Tolhurst et al. 2012; Yadav et al. 2013). There is limited data available regarding human studies, but few that is available suggests that supplementation of SCFAs mixture increases the levels of postprandial plasma peptide YY in subjects that were obese (Canfora et al. 2017). Figure 12 depicts some of the metabolic pathways in association with the occurrence of some ailments.

Industrial applications of SCFAs

Owing to the antimicrobial properties of SCFAs, they are more often utilized by food manufacturers and processors to ensure food safety (Figure 13). They are incorporated into various food products to inhibit microbes' pathogenic growth (Ricke 2003). Furthermore, various studies have been conducted regarding the addition of SCFAs to poultry

feed in order to control colonization of *Salmonella* as unhygienic poultry is thought to be the viable source of causing *Salmonella* infections in human (Callaway et al. 2008; Cox and Pavic 2010; Defoirdt et al. 2009; Jones 2011; Wales, Allen, and Davies 2010). Thus, supplementation of SCFAs to livestock feed has demonstrated the potential to avert shedding and colonization of pathogenic microorganisms hence minimizing the risk associated with their infections. Nevertheless, other acceptable workplace practices must also be adopted to ensure maximum food safety, as the addition of SCFAs to livestock diet can just minimize the chances of *Salmonella* contamination (Van Immerseel et al. 2003). SCFAs and gut microbiota have been reported to have a beneficial effect on meat production and, therefore, could be employed in the meat rabbit industry (Fang et al. 2020).

Generally, prebiotics are compounds that are thought to be food for gut microbiota. Consumption of prebiotics results in gut microbiota modulation resulting in improved health perspectives (Gibson et al. 2004). NDCs like galactooligosaccharides, inulin, and fructooligosaccharides are to date the best-known type of prebiotics available commercially. According to the World Gastroenterology Organization recommendations, supplementing the diet with prebiotics results in health modulating characteristics and could lead to an increased population of gut microbiota (*Lactobacillus* & *bifidobacteria*) therefore increasing the production of SCFAs (Macfarlane, Steed, and Macfarlane 2008). The beneficial role of prebiotics may alter depending upon the composition of gut microbiota that could vary in diseased subjects. The diseased human might have deficient gut

microbiota, therefore decreasing prebiotics' efficiency (Schloissnig et al. 2013). This issue could be resolved by using the concept of synbiotics in which prebiotics are provided to a person along with probiotics hence ensuring the availability of desired health-promoting gut microbiota. Further insight in this matter might help reveal innovative strategies in preventing diseases and promoting human health. SCFAs production by gut microbiota predominantly acetate, butyrate, and propionate results from the colon's fermentation of prebiotics. The pH of the gut lumen is lowered due to the production of SCFAs acting as a source of energy for epithelial cells and modulation the inflammation (Pourabedin and Zhao 2015).

Conclusions and future perspectives

In vivo and ex vivo studies have shown significant results regarding the use of SCFAs, especially propionate, butyrate, & acetate, in treating colonic diseases. Production of SCFAs producing microbiota could be enhanced by using prebiotics and/or synbiotics hence improving the clinical conditions. The rate and site of SCFAs production in the gut could be vital to physiological concerns, and so human studies are quite necessary to understand and interpret the results of animal modellings correctly. Developing shreds of evidence have suggested that recently discovered receptors of SCFAs, i.e. G-protein coupled receptors (GPCRs) may implicate in diverse physiological functions, and their pharmacological variations may signify vital targets therapeutically. Nevertheless, translational pharmacological studies are limited due to a lack of selective ligands and variation in orthologs gene in different species. Interestingly, the gut microbiota-derived metabolites, specifically SCFAs, act as imperative molecular signals among the gut microbiome and host and molecules that regulate the host's cellular metabolism. Compiling evidence has supported the fact that SCFAs mediates the cellular functionality in local, peripheral, and intermediary tissues. The multidimensional activity of SCFAs proposes their critical role in shielding the host body against impaired metabolic control and inflammation that is linked with the modern lifestyle.

Utilization of SCFAs and anti-inflammatory medicines, prebiotics, probiotics, symbiotics or as pro-drugs in cancer, and as coated objects in improving the healing characteristics of mucosal post colonic surgery could open a new window of opportunity in the field of therapeutics. It is important to comprehend the application of SCFAs as metabolite regulating barrier functionality and inflammation in disease alleviation since they are an inexpensive approach for easy intervention at the community level. Bodyweight management through SCFAs has well experimented with animal models, and the unique potential of SCFAs in regulating the appetite could be an emerging opportunity for tackling obesity. Conclusively, all the scientific data appraised in this review gives an overview of chemical interactions of gut microbiota driving health and diseases. More elaborate studies are required to investigate further the potential of SCFAs in understanding the multifaceted

interactions occurring in the intestine to increase our capability to improve food safety and human health.

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