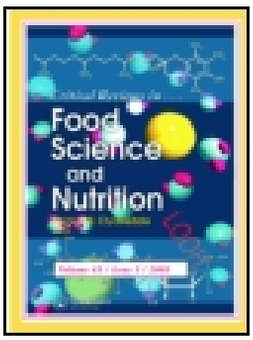

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Xiaodan Fu, Zhemin Liu, Changliang Zhu, Haijin Mou & Qing Kong (2018): Nondigestible carbohydrates, butyrate, and butyrate-producing bacteria, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2018.1542587

To link to this article: https://doi.org/10.1080/10408398.2018.1542587

Published online: 22 Dec 2018.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2018.1542587

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REVIEW

Nondigestible carbohydrates, butyrate, and butyrate-producing bacteria

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ABSTRACT

Nondigestible carbohydrates (NDCs) are fermentation substrates in the colon after escaping digestion in the upper gastrointestinal tract. Among NDCs, resistant starch is not hydrolyzed by pancreatic amylases but can be degraded by enzymes produced by large intestinal bacteria, including clostridia, bacteroides, and bifidobacteria. Nonstarch polysaccharides, such as pectin, guar gum, alginate, arabinoxylan, and inulin fructans, and nondigestible oligosaccharides and their derivatives, can also be fermented by beneficial bacteria in the large intestine. Butyrate is one of the most important metabolites produced through gastrointestinal microbial fermentation and functions as a major energy source for colonocytes by directly affecting the growth and differentiation of colonocytes. Moreover, butyrate has various physiological effects, including enhancement of intestinal barrier function and mucosal immunity. In this review, several representative NDCs are introduced, and their chemical components, structures, and physiological functions, including promotion of the proliferation of butyrate-producing bacteria and enhancement of butyrate production, are discussed. We also describe the strategies for achieving directional accumulation of colonic butyrate based on endogenous generation mechanisms.

KEYWORDS

Nondigestible carbohydrates; oligosaccharides; short-chain fatty acids; butyrate; butyrate-producing bacteria

Introduction

Studies on nondigestible carbohydrates (NDCs), including undigested plant polysaccharides, resistant starch (RS), and nondigestible oligosaccharides (NDOs), have attracted attention owing to the functions of these materials as dietary fibers (DFs) (Mussatto and Mancilha 2007; Smith and Tucker 2011; Holscher 2017). Human enzymes are capable of degrading only a few glycosidic linkages present in carbohydrates; however, intestinal bacteria possess many enzymes, including glycoside hydrolases, polysaccharide lyases, glycosyltransferases, and carbohydrate esterases, that are necessary for carbohydrate utilization (Englyst, Hay, and Macfarlane 1987; Lombard et al. 2014). Thus, NDCs can escape digestion in the host gastrointestinal tract to be metabolized by the microbiota in the cecum and colon (Ning et al. 2017). The metabolism of NDCs generate a variety of products, including short-chain fatty acids (SCFAs; e.g., acetate, propionate, and butyrate), gases (e.g., H_2, H_2S, CO_2, and CH_4), and organic acids (e.g., lactate, succinate, and pyruvate), which affect the host health to different extents (Macfarlane and Macfarlane 2012; Koh et al. 2016).

SCFAs, primarily acetate, propionate, and butyrate, have been estimated to provide approximately 60–70% of the energy requirements of colonic epithelial cells (Brahe, Astrup, and Larsen 2013). Specifically, the four-carbon SCFA butyrate is the major energy source for colonocytes, directly affecting the growth and differentiation of these cells (Jacobi and Odle 2012; Chen et al. 2015). Butyrate has been shown to play an important role in modulating immune and inflammatory responses and intestinal barrier function and in preventing colon cancers (Hamer et al. 2008; Elamin et al. 2013). Furthermore, recent studies have shown that NDCs consumption and dietary butyrate supplementation have beneficial effects on health by decreasing adiposity and improving insulin sensitivity (McNabney and Henagan 2017; Henagan et al. 2015).

In recent years, specific gut microbiota has attracted attention owing to their important roles in gut metabolism and homeostasis. In particularly, butyrogenic bacteria from within the *Firmicutes/Clostridium* clusters IV and XIVa have been taken as probiotics to increase colonic butyrate levels and optimize gut health (Scott et al. 2014; Hossain, Begum, and Kim 2015). Various strategies are available to enhance butyrate levels in the distal intestine. Supplementation with NDCs, such as RS (Brouns, Kettlitz, and Arrigoni 2002), psyllium fiber (Marteau et al. 1994), and guar gum (Pylkas, Juneja, and Slavin 2005), is another widely recognized approach. Butyrate production of NDCs can be influenced by many factors, such as the solubility, the distribution of chain lengths, branching and substituents, the monomeric carbohydrate composition, and linkage type between monomers (Karppinen et al. 2000; Henningsson, Björck, and Nyman 2002; Nilsson and Nyman 2005). Additionally, cross-feeding interactions between bacteria also affect colonic fermentation through modulating microbial mutualistic symbiosis and competitive fitness (Morrison and Preston 2016). However, the current understanding on the

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composition and metabolism of intestinal microbiota is still insufficient, which limits the application of this approach.

In this review, we summarize recent studies on NDCs with butyrogenic effects, factors affecting butyrate production, and physiological effects and mechanism of butyrate. Based on our analysis, the strategies of combining different NDCs and probiotic bacterial strains related with butyrate-production can be potentially meaningful to achieve directional accumulation of colonic butyrate.

Butyrate production and physiological effects

Butyrate production from NDCs

The human large intestine contains a very dense microbial ($>10^{11}$ bacteria per gram) community composed largely of a metabolically active microbiota (Flint et al. 2007). This community plays an important role in health and largely depends on dietary carbohydrate as an energy source. Most of these carbohydrates cannot be degraded by the host and are therefore broken down by the gut microbiota owing to their more excellent degradative enzymes and metabolic capabilities than their hosts (Flint et al. 2008; Kurokawa et al. 2007). Most of the dietary carbohydrates that reach the large intestine are generally insoluble fragments of plant fiber, which largely consists of plant cell-wall polysaccharides and starch particles, as well as oligosaccharides and storage polysaccharides (Flint et al. 2008). However, only a few gut bacteria are available to degrade the insoluble substrates. Specialized primary degraders, typically cellulolytic bacteria, are able to release a wider range of solubilized products (e.g. polysaccharides and oligosaccharides) from complex polymers during degradation, providing substrates for the secondary degraders through cross-feeding (Robert and Bernalier-Donadille 2003).

Cross-feeding is a central metabolic mechanism in microbial communities through which the solubilized and partially breakdown products are utilized by secondary degraders including bifidobacteria to form other metabolic products such as acetate, lactate, succinate, and branched chain fatty acids (Flint et al. 2007; Belenguer et al. 2006). Reutilization of the fermentation products is also important in the human large intestine. The fermentation of carbohydrates by bifidobacteria yields large quantities of acetate and lactate, which can be utilized by other species such as butyrate-producing *Roseburia* and *Faecalibacterium prausnitzii* to produce butyrate. For example, co-culture of the lactate-utilizing strain, *Eubacterium hallii*, with the starch-utilizing strain, *Bifidobacterium adolescentis*, promotes the accumulation of butyrate via cross-feeding (Belenguer et al. 2006). This microbial cooperation is likely to play a major role in the intestinal microbial ecology.

NDCs are important sources for butyrate fermentation by endogenous butyrate-producing bacteria, which are widely distributed in the human cecum and colon (van der Waaij et al. 2005). However, butyrogenic effects are likely to be influenced by the features of NDCs, including the solubility, the monomeric carbohydrate composition, the distribution of chain lengths, branching and substituents, and also the inter-individual variations in microbiota composition (Karppinen et al. 2000; Henningsson, Björck, and Nyman 2002; Nilsson and Nyman 2005; Louis et al. 2010). Moreover, the gut bacteria differ in their possession of degradative enzymes and transport systems, which likely determines the substrate preference and competitive ability of a given bacteria, and consequently the butyrate-producing ability (Flint 2004; van der Meulen et al. 2006).

Previously described butyrate-producing bacteria in the human gastrointestinal intestinal tract are commonly distributed in the phylum Firmicutes and the order Clostridiales (Table. 1). The majority of these producers belong to four families: Clostridiaceae, Eubacteriaceae, Lachnospiraceae, and Ruminococcaceae; however, not all the members within these families are butyrogenic (Duncan et al. 2002; Louis et al. 2004; Louis and Flint 2009; Vital, Howe, and Tiedje 2014). Members within other families such as Veillonellaceae (e.g., *Megasphaera elsdenii*) and Thermoanaerobacterales Family III (e.g., *Caldocellum saccharolyticum*) have also been identified as butyrate producers (Louis et al. 2004; Tsukahara et al. 2002). Most butyrate producers in the order Clostridiales are widely distributed across several clusters including clusters IV, XIVa, XVI, and I. Among them, two of the most important groups, *F. prausnitzii* (clostridial cluster IV) and *Eubacterium rectale* (clostridial cluster XIVa), have been studied extensively because they typically constitute up to 12 − 14% of the total gut microbiota in fecal samples of healthy adults based on 16S rRNA gene sequencing (Walker et al., 2014). Moreover, other typical butyrogenic species are also widely distributed across cluster XIVa (e.g., *Roseburia* spp., *Anaerostipes* spp., *Clostridium* spp., *Ruminococcus* spp., *Coprococcus* spp., *Butyrivibrio* spp.) and cluster IV (e.g., *Butyricicoccus pullicaecorum*, *Subdoligranulum variabile*, *Anaerotruncus colihominis*, and *Papillibacter cinnamivorans*) (Louis and Flint 2009; Vital, Howe, and Tiedje 2014; van den Abbeele et al. 2013).

Recently, novel butyrate-producing strains have been isolated from the intestinal tract of humans. Fecal strain 3BBH22^{T}, named *Lawsonibacter asaccharolyticus*, was proposed as a novel species in a novel genus of the family Ruminococcaceae. The genome of this strain revealed the expression of butyrate kinase (Sakamoto et al. 2018). *Intestinimonas butyriciproducens* AF211, isolated from the human gut, encodes butyryl-CoA: acetyl-CoA transferases as the key enzymes for butyrate production (Bui et al. 2016). Based on high-throughput sequencing, potential butyrate producers can be identified through metagenome functional predication. According to Esquivel-Elizondo et al. (2017), Prevotellaceae, Clostridiaceae, and Lactobacillaceae were the potential butyrate producers in the constructed bioreactor using high-throughput 16S rRNA gene sequencing techniques in combination with chemical analysis. Moreover, *Actinobacteria*, *Bacteroidetes*, *Fusobacteria*, *Proteobacteria*, *Spirochaetes*, and *Thermotogae* were also identified as potential butyrate producers by analysis of metagenomic data from 15 fecal samples of healthy individuals provided by the HMP (Human Micro-biome Project) (Vital, Howe, and Tiedje 2014); however, specific biochemical tests, such as metabolic flux studies, are needed to verify this prediction.

Table 1. The typical butyrate-producing bacteria in human gut.

Bacterial species	Clostridial cluster	Familiy	Acetate utilization	Lactate utilization	Butyrate kinase	Reference
Faecalibacterium prausnitzi	IV	Clostridiaceae	+			Louis et al. 2004
Roseburia cecicola	XIVa	Lachnospiraceae	+			Duncan et al. 2002; Louis and Flint 2009
Roseburia faecis	XIVa		+			Duncan et al. 2002; Louis and Flint2009
Roseburia hominis	XIVa		+			Duncan et al. 2002; Louis and Flint2009
Roseburia intestinalis	XIVa		+			Duncan et al. 2002; Louis and Flint2009
Roseburia inulinivorans	XIVa		+			Duncan et al. 2002; Louis and Flint 2009
Eubacterium cylindroides	XVI	Eubacteriaceae	+			Louis et al. 2004
Eubacterium hallii	XIVa		+	+		Louis et al. 2004
Eubacterium limosum	XIVa			+		Kanauchi et al. 1999
Eubacterium ramulus	XIVa		+			Louis et al. 2004
Eubacterium rectale	XIVa		+			Louis and Flint 2009
Eubacterium ruminantium	XIVa		+		+	Louis et al. 2004
Eubacterium ventriosum	XIVa		+			van den Abbeele et al. 2013
Clostridium acetobutylicum	I	Clostridiaceae			+	Yoo et al. 2017
Clostridium butyricum	I				+	Vital, Howe, and Tiedje 2014
Clostridium hathewayi	XIVa		+			Louis et al. 2004
Clostridium indolis	XIVa		+			Louis et al. 2004
Clostridium nexile	XIVa		+		+	Louis et al. 2004
Clostridium orbiscidens	IV		+			Levine et al. 2013
Clostridium saccharobutylicum	I				+	Huang, Liebl, and Ehrenreich 2018
Clostridium symbiosum	XIVa		+			Vital, Howe, and Tiedje 2014
Clostridium tyrobutyricum	I				+	Jiang et al. 2013
Anaerostipes butyraticus	XIVa	Lachnospiraceae		+		Louis and Flint 2009
Anaerostipes caccae	XIVa		+	+		Louis et al. 2004
Anaerostipes hadrus	XIVa		+	+		Louis and Flint 2009
Anaerostipes rhamnosivorans	XIVa		+	+		Bui, de Vos, and Plugge 2014
Ruminococcus gnavus	XIVa	Ruminococcaceae	+			Louis et al. 2004
Ruminococcus obeum	XIVa		+			Louis et al. 2004
Coprococcus catus	XIVa	Lachnospiraceae	+	+		Louis and Flint 2009
Coprococcus comes	XIVa				+	Louis and Flint 2009
Coprococcus eutactus	XIVa		+		+	Duncan et al. 2002
Butyrivibrio crossotus	XIVa	Lachnospiraceae			+	Meehan and Beiko 2014
Butyrivibrio fibrisolvens	XIVa		+			Diez-Gonzalez et al. 1999
Butyrivibrio proteoclasticus	XIVa				+	Meehan and Beiko 2014
Shuttleworthia satelles	XIVa	Lachnospiraceae			+	Meehan and Beiko 2014
Subdoligranulum variabile	IV	Clostridiaceae	+			Holmstrøm et al. 2004; Vital, Howe, and Tiedje 2014
Anaerotruncus colihominis	IV	Clostridiaceae	+			Lau et al. 2006; Vital, Howe, and Tiedje 2014
Butyricicoccus pullicaecorum	IV	Clostridiaceae	+			Eeckhaut et al. 2011; Eeckhaut et al. 2013
Papillibacter cinnamivorans	IV	Ruminococcaceae	ND	ND	ND	van den Abbeele et al. 2013
Caldocellum saccharolyticum	X	Thermoanaerobacterales Family III	+			Louis et al. 2004
Megasphaera elsdenii	IX	Veillonellaceae	+	+		Tsukahara et al. 2002

ND, not determined.

The utilization of complex carbohydrates varies within different species and even within strains. Regarding the fermentation of NDCs in the human intestine, only a few butyrate-producers are able to degrade NDCs directly. *Roseburia inulinivorans* encodes β-fructofuranosidase, which degrades both inulin and fructooligosaccharide (FOS)

(Falony et al. 2009), while *F. prausnitzii* degrades inulin and pectin (Duncan et al. 2002; Lopez-Siles et al. 2012). Besides, RS, xylo-oligosaccharides (XOS), and arabinoxylan-oligosaccharides (AXOS) can also provide substrates for other butyrate-producers belonging to clostridial clusters IV and XIVa (Louis and Flint, 2009; Scott et al. 2014; Rivière et al. 2015). However, most of the butyrate-producers have no preferential carbohydrate degradation mechanism for degrading oligo- and polysaccharides into monosaccharides. Specialized primary degraders (e.g. bifidobacteria/lactobacilli/bacteroides) produce various of enzymes to degrade the complex carbohydrates (Flint et al., 2012). Through cross-feeding, intermediates obtained by NDC breakdown and fermentation products from these primary degraders can provide substrates for butyrate-producers that are not able to degrade NDCs directly (Rogowski et al. 2015).

Among the pathways known for butyrate production using carbohydrates as substrates, the acetyl-CoA pathway is likely to be present in the majority of butyrate-producing bacteria, particularly members of the phylum Firmicutes (Louis and Flint 2009). Additionally, other pathways for butyrate production, including the lysine, succinate, and glutarate pathways, have also been found in different phyla, such as Firmicutes, Bacteroidetes, Fusobacteria, that use amino acids as major substrates (Vital, Howe, and Tiedje 2014; Bui et al. 2015). Once NDCs are degraded into monosaccharides, the pentoses and hexoses are converted to pyruvate through the Embden-Meyerhof-Parnas pathway or the pentose phosphate pathway, respectively. Pyruvate can be converted to acetyl-CoA by a pyruvate: ferredoxin oxidoreductase and/or by a pyruvate-formate lyase. Subsequently, two molecules of acetyl-CoA are converted to butyryl-CoA via a condensation reaction. Butyryl-CoA can be phosphorylated to form butyryl-phosphate via phospho-transbutyrylase and subsequently converted to butyrate via butyrate kinase (Louis and Flint 2017). However, only a few butyrate producers, including *Clostridium butyricum*, *Clostridium saccharobutylicum*, *Coprococcus eutactus*, and *Coprococcus comes*, are known to use a butyrate kinase to produce butyrate (Louis and Flint 2009; Vital, Howe, and Tiedje 2014; Huang, Liebl, and Ehrenreich 2018). Moreover, the CoA moiety of butyryl-CoA can be transferred to acetate via butyryl-CoA: acetyl-CoA transferase, leading to the formation of butyrate and acetyl-CoA. Butyryl-CoA: acetyl-CoA transferase appears to be the main pathway in the human bacterial flora, and remarkably, this pathway requires acetate through cross-feeding reactions (Morrison et al. 2006; Trachsel et al. 2016). Additionally, some butyrate producers, including *E. hallii*, *Anaerostipes butyraticus*, *Anaerostipes caccae*, *Anaerostipes hadrus*, *Anaerostipes rhamnosivorans*, and *M. elsdenii*, are able to convert lactate to pyruvate and then to butyrate, instead of carbohydrates, via either a butyrate kinase or butyryl-CoA: acetyl-CoA transferase (Bui, de Vos, and Plugge 2014; Duncan et al., 2004; Engels et al. 2016; Hashizume et al. 2003; Louis and Flint 2009). Another common butyrogenic pathway is the conversion of succinate to the butyrate precursor, crotonyl-CoA, which is subsequently transformed to butyrate (Ferreyra et al. 2014).

Physiological effects and mechanisms of butyrate

A growing number of investigations has confirmed the benefits of butyrate in host health (Fig. 1) (Guilloteau et al. 2010; Meijer et al. 2010; McNabney and Henagan 2017). Butyrate is the major energy source for colonocytes and contributes to the maintenance of intestinal homeostasis. Although the exact underlying mechanisms of action have not yet been elucidated, butyrate is believed to influence cell function through its regulation of gene expression (Daly and Shirazi-Beechey 2006; Davie 2003). A previous report has shown that butyrate activity involves the epigenetic regulation of gene expression through inhibition of histone deacetylase (HDAC) (Canani, Costanzo, and Leone 2012). This epigenetic regulation has been implicated to have anticarcinogenic and chemopreventive effects, neuroprotective effects, anti-inflammatory effects, and effects on obesity, insulin resistance, cardiovascular diseases, immunoregulation, and inherited disorders (Davie, 2003).

Butyrate is able to exert a powerful effect on transepithelial ion transport (Canani et al. 2011). A study showed that colonic water, Na^+, K^+ and Cl^- secretions were significantly reduced by butyrate (Rabbani et al. 1999). Moreover, butyrate therapy, which stimulates the Cl^-/butyrate exchanger activity, was found to be beneficial in patients affected by congenital chloride diarrhea (Canani et al. 2004). Butyrate can act as an anti-inflammatory agent via inhibition of nuclear factor κB (NF-κB) activation, which results from the inhibition of HDAC (Inan et al. 2000). Adding to its anti-inflammation and anti-cancer roles, butyrate can directly activate G-protein coupled receptors (GPCR) to maintain the balance of tolerance to commensals and immunity to pathogenic bacteria in intestinal immune system (Koh et al. 2016; Singh et al. 2014). Intake of inulin and OF has beneficial effects on the gut-associated lymphoid tissue, which may result from the enhanced production of immunoregulatory SCFAs and perhaps other bacterial metabolites (Seifert and Watzl 2007). Butyrate can influence upper gut motility and satiety by increasing the expression of peptide YY and proglucagon in rat epithelial cells (Zhou et al. 2006).

Growing evidence indicates the presence of extensive communication between the brain and the gut via the gut-brain axis (Stilling et al. 2016). Butyrate can increase the proportion of cholinergic enteric neurons via epigenetic regulation, to affect gut hormone release in enteric nervous system (ENS), and stimulate the vagus nerve to elicit endocrine signaling; both impacting brain function (van de Wouw et al. 2017). NDCs and butyrate also have positive effects on metabolic diseases. One study showed that guar gum treatment decreased markers of the metabolic syndrome and gene expression related to gluconeogenesis and fatty acid synthesis in a dose-dependent manner (den Besten et al. 2014). Butyrate can also prevent and treat diet-induced obesity and insulin resistance in mouse models. It is thought to do so via the stimulation of peroxisome proliferator-activated receptor (PPAR) coactivator (PGC-1α) activity and the secretion of glucagon-like peptide 1 (GLP-1) in the gut, which stimulates insulin secretion, reduces the rate of gastric emptying, increases insulin sensitivity and decreases energy intake (Freeland et al. 2010; Gao et al. 2009; Li et al. 2018).

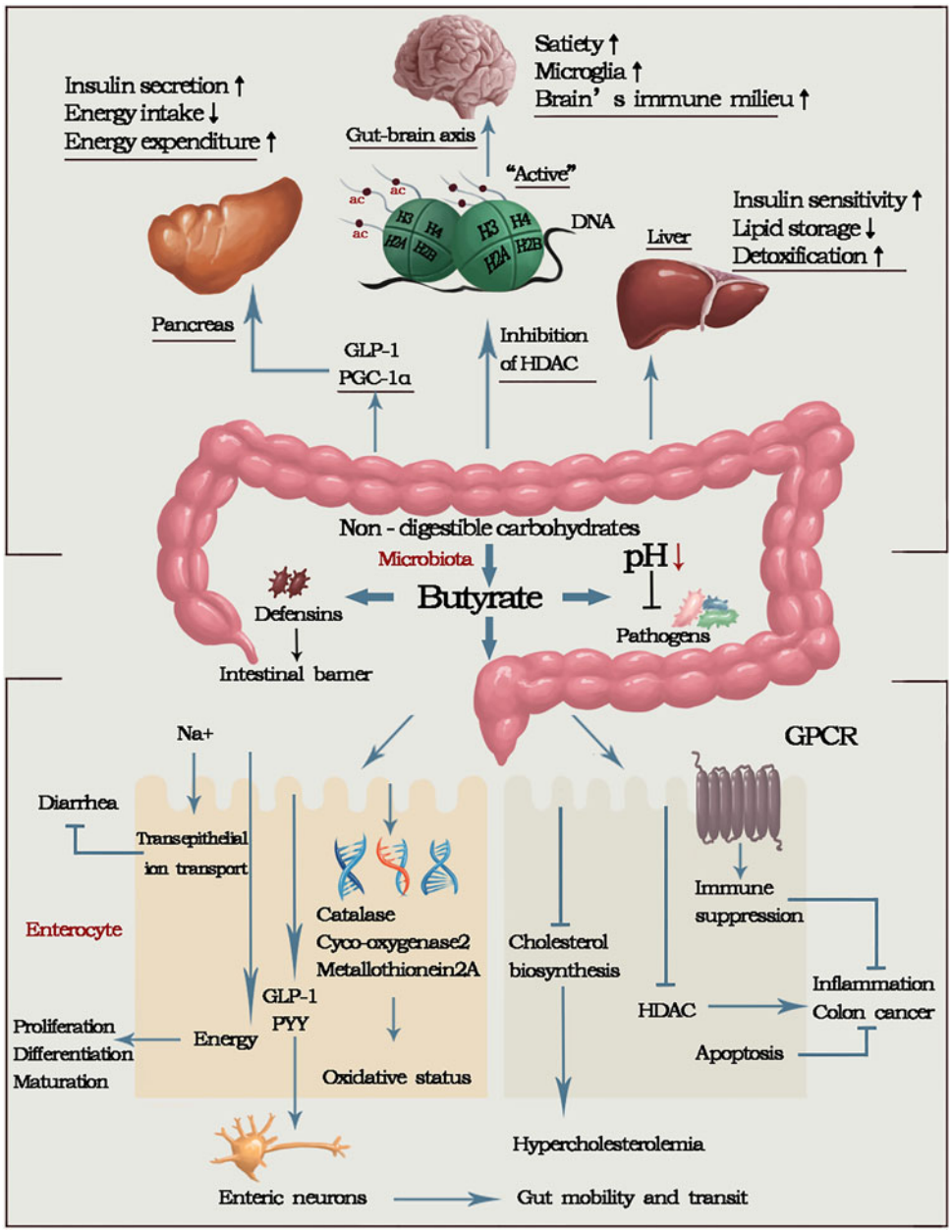

Figure 1. Multiple beneficial effects of butyrate at intestinal and extraintestinal level. Fermentation of NDCs leads to butyrate production. Luminal butyrate inhibits the growth of pathogens and strengthens the function of intestinal barrier. Butyrate can enter the enterocytes (two cells outlined at the bottom of the figure) and act as an energy source or an HDAC inhibitor. Butyrate affects satiety and gut mobility and transit through increasing the expression of PYY and GLP-1. Butyrate exerts anti-inflammatory and anti-cancer effects via immune suppressive mechanisms, apoptosis and HDAC inhibition. Furthermore, butyrate can inhibit the intestinal cholesterol biosynthesis, diarrhea and oxidative status. Butyrate can also affect the pancreas, liver and brain, inducing overall beneficial metabolic effects, such as insulin secretion, insulin sensitivity, energy expenditure, and shaping the brain's immune milieu.

Based on these reports, it is clear that butyrate plays key functional roles in the maintenance of intestinal homeostasis as well as in overall health status. Further research is critical to minimize the adverse effects of butyrate, such as its potential contribution to obesity (Liu et al. 2018) and expand its use in clinical applications together with the administration of NDCs.

NDCs beneficial for the production of butyrate

To date, numerous NDCs have been reported, and some have been commercially developed and applied as food additive ingredients and functional factors. As introduced above, NDCs enter the metabolism of primary degraders, which subsequently affects the fermentation of secondary degrader in general, especially the butyrate formation by butyrogenic bacteria. In this section, several representative NDCs are introduced, including their fermentability and butyrate production ability (Table 2).

Water-insoluble polysaccharides

Dietary polysaccharide sometimes enters the gut in the form of insoluble particles. A few gut bacteria are directly engaged

Table 2. NDCs: Structures and benefits for intestinal microflora and butyrate production.

Source of carbohydrate	Component and structure	Function and application	Intestinal microbes with fermentability	SCFA production	Reference
Cereal bran	Combination of polymers, such as arabinoxylan (AX), β-glucan, fructan, cellulose and lignin	Help for gut transit, decrease on tumors, formation of butyrate and prebiotic effect	*Bifidobacterium* spp., *E. xylanophilum, E. rectale, B. fibrisolvens, R. faecis, R. intestinalis*	Formation of butyrate depends on its physical status	Govers et al. 1999 Lampe et al. 1993 Dhingra et al. 2012 Damen et al. 2011 Louis, Hold, and Flint 2014 Duncan et al. 2016
Psyllium polysaccharide	Highly branched arabinoxylan with xylose as the backbone, and arabinose and xylose as the side chains	Effective for irritable bowel diseases, inflammatory bowel disease and ulcerative colitis	Bifidobacteria	Increase fecal concentrations of butyrate by 42 % and total SCFAs by 25%	Bijkerk et al. 2004Elli et al. 2008Nordgaard et al. 1996
Alginate	Composed by mannuronic acid and guluronic acid	Used as food additives and textile processing aids	*B. ovatus, B. xylanisolvens, B. thetaiotaomicron, Cl. orbiscindens, R. gnavus, E. lenta, Bifidobacterium* spp. and *Lactobacillus* spp.	Algal fiber and Na-alginate are partly metabolized to SCFAs	Li et al. 2017An et al. 2013 Ramnani et al. 2012Wang, et al. 2006Michel et al. 1996
Pectin	Partially methyl esterified (1-4)-linked α-D-galacturonic acid; repeating disaccharide [-2)-α-L-Rhap-(1-4)-α-D-GalpA-(1-] as backbone	Modulation of gut microbiota, anti-inflammatory effect	Ruminococcaceae and Succinivibrionaceae families	Increase fecal concentrations of butyrate and total SCFAs	Tian et al. 2017 Onumpai et al. 2011 Bianchi et al. 2018
Chitin and chitosan	Water-insoluble polysaccharide composed by linear β-1,4-linked N-acetylglucosamine	Ingredient for functional food and cosmetics, regulation on gut microbiota	*L. brevis, L. casei, Bif. bifidum* and *Bif. breve*	Oligosaccharides show better effects on production of SCFAs	Vernazza, Gibson, and Rastall 2005, Lee et al. 2002 Nurhayati et al. 2016
Germinated barley	Containing glutamine-rich protein and hemicelluloses-rich fiber	Nutraceutical treatment of ulcerative colitis, mitigation colonic mucosal damage and bloody diarrhea	*Bif. breve, Bif. longum, L. acidophilus, Cl. butyricum* and *Eubacterium* spp.	Therapeutic effects for colitis depend mainly on increased SCFAs, especially butyrate	Kanauchi et al. 2001 Kanauchi et al. 1999 Araki, Andoh, et al. 2000
Partially hydrolyzed guar gum	Galactomannan, possessing linear chain of β-D-mannopyranosyl units with α-D-galactopyranosyl residues as side chains	Therapy treatment in hypercholesterolemia, hyperglycemia and obesity, cholesterol and glucose lowering effects, weight loss	*B. ovatus, Cl. coccoides, Cl. butyricum, P. productus, Bif. dentium* and *Lactobacillus* spp.	Produce acetate as the major SCFAs, followed by butyrate	Butt et al. 2007 Okubo et al. 1994Hartemink, Schoustra, and Rombouts 1999
Inulin fructans	β-(2-1)-linked fructans dietary fiber, including inulin, FOS and OF	Selective stimulation of bifidobacteria, modulation of lipid metabolism	*Cl. butyricum, Cl. ramosum, F. prausnitzii, Roseburia* spp. *Eubacterium* spp.and *Bifidobacterium* spp.	Selectively stimulate the bacterial conversion of acetate and lactate to butyrate	Roberfroid et al. 2010 Biedrzycka and Bielecka 2004 Rossi et al. 2005194 Louis et al. 2007 Ramirez-Farias et al. 2009
Resistant starch	Starch portion not absorbed in the small intestine	Reverse infectious diarrhea, reduce insulin resistance, prevent colorectal cancer	*R. bromii, E. rectale, F. prausnitzii, Bifidobacterium* spp.	Produce high yield of butyrate (20–28% in SCFAs); Produce butyrate more distally in colon	Ze et al. 2012Walker et al. 2011 Leitch et al. 2007 Brouns, Kettlitz, and Arrigoni 2002Haenen et al. 2013 Martin et al. 2000
Isomalt	α-D-glucopyranosido-1,6-mannitol and α-D-glucopyranosido-1,6-sorbitol	Prebiotic carbohydrate	*Bif. adolescentis, Bif. catenulatum, Bif. infantis* and *Cl. perfringens*	Increase cecal concentrations of SCFAs	Fu et al. 1999 Djouzi and Andrieux 1997
Galacto-oligosaccharide	From lactose by transgalactosylation	Prebiotic carbohydrate	*Bifidobacterium* spp. and *F. prausnitzii*	Promote SCFAs production	Scott et al. 2014 Liu et al. 2017 Davis et al. 2011
Lactulose	Synthetic disaccharide (galactofructose)	Prebiotic oligosaccharide	Bifidobacteria and lactobacilli	Promote SCFAs production	Schumann2002, Krueger et al. 2002
Acarbose	Pseudo-oligosaccharide	Treatment for diabetes mellitus type 2	Butyrate-producing bacteria	Increase the colonic concentration of butyrate	Weaver et al. 1992 Holt et al. 1996 Weaver et al. 1997

in the breakdown of insoluble substrates, such as cellulose and hemicellulose. The breakdown products then enter the further metabolism process resulting the production of SCFA. Generally, water-insoluble NDCs are hydrolyzed to smaller soluble fragments, and are then fermented into SCFA and gases by secondary degraders including butyrate-producing bacteria in gut (Robert and Bernalier-Donadille 2003). However, the water-insoluble NDCs are generally more resistant to colonic fermentation than soluble NDCs. The effect of solubility on NDCs fermentation will be discussed in the followed chapter.

Cereal dietary fiber (DF) has long been considered an important component of the healthy human diet (Flint et al. 2012; Smith and Tucker 2011). The cereal DF complex is composed of a combination of polymers, including arabinoxylan (AX), β-glucan, fructan, cellulose, and lignin. The structure, content, and interactions of specific components of grains may change depending on the processing (Guillon and Champ 2000). Cereal DF has heterogeneous chemical structures and is composed of water-soluble DF (SDF) and insoluble DF (IDF). In all cereal bran, the IDF is predominant especially in maize bran and wheat bran, which is remarkably different from SDF in the promotion of beneficial bacterial growth and SCFA production (Vitaglione et al. 2008). It cannot be digested by human digestive enzymes; however, this material affects gut transit and shifts the main site of starch fermentation distally down the intestine (Govers et al. 1999). Cereal bran can also affect health through its prebiotic effects and fermentation in the large intestine to yield SCFAs (Dhingra et al. 2012). Damen et al. reported that water unextractable cereal arabinoxylan is partially fermented in the colon and increases the levels of butyrate and butyrate-producing *Roseburia/E. rectale* spp. (Damen et al. 2011). The Lachnospiraceae isolates *E. rectale*, *Butyrivibrio fibrisolvens*, *Roseburia faecis*, and *Roseburia intestinalis* produce butyrate as their main fermentation product after a 7-day incubation on wheat bran (Duncan et al. 2016). Feeding of wheat bran can decrease the occurrence of chemically induced tumors in rodents, which is mainly ascribed to the stimulation of butyrate formation via wheat bran fermentation in the large intestine (Damen et al. 2011; Louis, Hold, and Flint 2014). The formation of butyrate and the growth of butyrate-producing bacteria closely depend on the physical status of wheat bran. D'hoe et al. (2018) assessed the prebiotic potential of selected wheat bran fractions using wheat bran with different physical statuses as carbon sources, and the results show that fermentation using ultrafine, soluble, and total wheat bran can stimulate the growth of *Bifidobacterium* species, whereas aleurone selectively stimulates the growth of butyrate-producing *Roseburia*. Furthermore, wheat bran is more slowly fermented than oat bran, providing higher amounts of butyrate in the distal colon in rats, and strongly enriching *Eubacterium xylanophilum* and *Butyrivibrio* spp. during human fecal fermentation (Duncan et al. 2016; Reddy et al. 2000).

Germinated barley contains glutamine-rich protein and hemicellulose-rich fiber, and is another water-insoluble polysaccharide (Bamba et al. 2002). Both in experimental models and clinical trials, germinated barley foodstuff (GBF) treatment has shown potential for attenuating the symptoms of colitis (Kanauchi et al. 1998). According to Kanauchi et al. (2001), DF fraction of GBF attenuates mucosal damage and diarrhea and accelerates repair of the colonic mucosa in an animal model, which may be associated with increased concentrations of SCFAs, particularly butyrate. Administration of GBF or its fiber fraction results in a significant increase in butyrate production and butyrate-producing bacteria proliferation (Koh and Kim 2011). However, accurate understanding of microbial ecology and the breakdown of complex insoluble fibers in the human colon is still needed.

Water-soluble neutral polysaccharides

Water-soluble polysaccharides are much easier to be utilized by the gut bacteria than water-insoluble polysaccharides. Several water-soluble neutral polysaccharides, such as psyllium, partially hydrolyzed guar gum (PHGG), inulin fructan, and RS, are reported to be beneficial for butyrate production in the gut.

Psyllium has been used as a DF supplement for many years (Thakur and Thakur 2014). The most abundant polysaccharide in psyllium is complex heteroxylan, which is a highly branched arabinoxylan with xylose as the backbone and arabinose and xylose as the side chains (Marlett and Fischer 2003). Psyllium supplementation has been shown to be effective for the treatment of irritable bowel disease, inflammatory bowel disease, and ulcerative colitis (Bijkerk et al. 2004). Anaerobic fermentation of psyllium fiber in the intestine results in considerable production of SCFAs (Pylkas, Juneja, and Slavin 2005). Oral intake of *Plantago ovata* seeds adapts the colonic flora to increase fecal concentrations of butyrate, acetate, propionate, and total SFCAs by 42%, 25%, 28%, and 25%, respectively. However, SCFA production returns to pretreatment levels after discontinuation of additional fiber intake, demonstrating that the effects depended on the continuity of treatment (Nordgaard et al. 1996). Fernández-Bañares et al. (1999) also found that fecal levels of butyrate were increased in patients consuming *Plantago ovata* seeds, which was helpful for the maintenance of disease remission in patients with ulcerative colitis.

Guar gum is derived from the seeds of guar or cluster bean, with the botanical name *Cyamopsis tetragonoloba* (Prem et al. 2005). Guar gum is a complex carbohydrate polymer with a high molecular weight, usually called galactomannan, and possesses a linear chain of (1→4)-linked β-D-mannopyranosyl units with (1→6)-linked α-D-galactopyranosyl residues as side chains (Mudgil, Barak, and Khatkar 2014). The physiological functions of PHGG have been extensively studied. PHGG administration *in vitro* results in moderate growth of *Bacteriodes ovatus*, *Clostridium coccoides*, *Cl. butyricum*, and *Peptostreptococcus productus* (Okubo et al. 1994). Moreover, PHGG intake in healthy human volunteers significantly increases the numbers of *Bifidobacterium* spp. and *Lactobacillus* spp. in fecal microflora (Okubo et al. 1994). Similar results were also obtained by Hartemink et al. (1999), demonstrating that *Cl.*

butyricum and *Bifidobacterium dentium* are the main guar-degrading species in the human large intestine. Among the degraders, *Cl. butyricum* shows faster degradation speed than other species under simulated physiological conditions. The strains can degrade guar gum completely and leave butyrate (28% of total SCFAs) as the main functional products (Hartemink, Schoustra, and Rombouts 1999).

Inulin and its low-molecular weight derivatives, oligofructose (OF) and FOSs, are usually called β-(2-1)-fructans DFs and have been studied extensively based on their specifically bifidogenic effects (Roberfroid, van Loo, and Gibson 1998). Inulin and OF stimulate the growth of *Bifidobacterium* and can be completely metabolized by the microbial flora (Meyer and Stasse-Wolthuis 2009; Roberfroid et al. 2010). Several studies have reported that the majority of *Bifidobacterium* species possess intracellular β-(2-1)-fructan-hydrolyase activity, i.e., inulinase (β-fructo-furanosidase), which cleaves the β-(2-1)-glucosidic bond present in inulin and OF (Biedrzycka and Bielecka 2004; Rossi et al. 2005). This process promotes the fermentation of inulin and OF by *Bifidobacterium* and the production of butyrate from lactate and acetate (Louis et al. 2007). Besides, the degradation rate of oligomers (DP <10) is approximately twice that of molecules with a higher DP. The utilization of FOS and inulin by 55 *Bifidobacterium* strains demonstrated that FOSs are fermented by most strains, whereas only eight strains grow when inulin is used as the carbon source, suggesting that the fermentability is different among inulin-type fructans (Rossi et al. 2005). This work also reported that butyrate is the major fermentation product of inulin, whereas mostly acetate and lactate are produced from FOSs. *F. prausnitzii* and *Eubacterium* spp. are increased in response to inulin or OF ingestion (Louis et al. 2010; Ramirez-Farias et al. 2009). However, *Cl. butyricum* and *Clostridium ramosum* metabolize FOSs well, showing even higher fermentation rate than other intestinal bacteria (Biedrzycka and Bielecka 2004). Another work performed by Morrison et al. (2006) proved that OF is mainly fermented by acetate and lactate-producing bacteria rather than butyrate-producing bacteria, with *Bifidobacterium* and *Lactobacillus* as the main species. Subsequently, cross-feeding promotes the extracellular acetate and lactate to convert to butyrate by butyrate-producing bacteria, such as *F. prausnitzii* and *Roseburia* spp. (Duncan et al. 2004). Thus, OF selectively stimulates the bacterial conversion of acetate and lactate to butyrate, with 80% of butyrate derived from interconversion of extracellular acetate and lactate (Morrison et al. 2006). The states from different researchers prove that the butyrate-producing ability from inulin and its low-molecular weight derivatives are different. More works *in vivo* are still needed to illuminate their prebiotic effects under the complex intestinal ecological environment.

RS is the starch portion that is not absorbed in the small intestine but is fermented in the large intestine (Yang et al. 2017). RS fermentation is believed to reverse infectious diarrhea (Niderman-Meyer et al. 2010; Ramakrishna et al. 2000), reduce insulin resistance (Robertson et al. 2005), and prevent colorectal cancer (Leu et al. 2009; Young et al. 2005). Fermentation of RSs usually leads to a high yield of butyrate (molar quantity in SCFAs: 20–28%) (Brouns, Kettlitz, and Arrigoni 2002). Dietary supplementation with RSs (unmodified potato starch, ungelatinized starch) increases the relative abundance of RS-degrading organisms, *Bif. adolescentis* and *Ruminococcus bromii*, as well as the butyrogenic microbe *E. rectale* (Venkataraman et al. 2016). In animal tests, RSs were completely degraded in the cecum, stimulating the growth of *F. prausnitzii*, whereas potentially pathogenic Gammaproteobacteria, including *Escherichia coli* and *Pseudomonas* spp. was reduced (Haenen et al. 2013). Several studies have suggested that retrograded RS (RS3) is one of the most powerful butyrate-producing substrates (Bird, Brown, and Topping 2000). Compared with indigestible short-chain oligosaccharides (FOSs and xylo-oligosaccharides [XOSs]), the fermentation of RS is relatively slow. Thus, butyrate produced from RS3 was more distally fermented in the colon, thereby improving the luminal conditions in the distal colonic regions where tumors most commonly occur (Martin et al. 2000).

Water-soluble acid polysaccharides

Acid polysaccharides are a family of polyanionic compounds usually containing uronic acid or sulfate groups. These polysaccharides are not common in terrestrial materials, but can be found in most of the seaweeds (marine macroalgae), named alginate, fucoidan, agar and carrageenan. Alginate is the major structural polysaccharide of brown macroalgae and is widely used as a food additive and textile processing aid. It also shows potential applications as a functional food ingredient relating to its beneficial effects on gut ecology (Holdt and Kraan 2011; O'Sullivan et al. 2010). It is a high-molecular-weight polymer composed of different ratios of mannuronic acid and guluronic acid. Usually, complex polysaccharides including alginate are not thought to be ideal as prebiotics since their fermentability is weak in the normal human gut. However, several reports have shown that alginate is readily fermented by human gut bacteria, including *B. ovatus*, *Bacteroides xylanisolvens*, and *Bacteroides thetaiotaomicron* (Li et al. 2017). Specifically, *B. ovatus* produces β-mannuronan lyase and α-guluronan lyase, which are the key enzymes for the fermentation of alginate. The prebiotic effects of low-molecular-weight derivatives of alginate, including mannuronic acid oligosaccharides and guluronic acid oligosaccharides, have also been reported. Alginate supplementation improves the fermentation ability of intestinal microbiota and increases the abundance of *Clostridium orbiscindens*, *Ruminococcus gnavus*, *Eggerthella lenta*, and *Clostridiales* spp. (An et al. 2013). Moreover, the growth of *Bifidobacterium* spp. and *Lactobacillus* spp. in the gastrointestinal tract is also stimulated by alginate and its oligosaccharides to produce acetate and lactate (Ramnani et al. 2012; Wang et al. 2006). Fermentation of alginate by gut microbes is obviously beneficial for increasing the concentrations of butyrate or its metabolic precursors in the cecum. Other water-soluble acid polysaccharides from seaweed, such as

fucoidan, are also reported to increase butyrate concentration in feces (Lynch et al. 2010).

Pectins are another important water-soluble acid polysaccharide highly present in the cell walls of fruits and vegetables. The predominant structure in pectin is composed of partially methyl esterified (1-4)-linked α-D-galacturonic acid units; and a second structure is composed of repeating disaccharide [-2)-α-L-Rha*p*-(1-4)-α-D-Gal*p*A-(1-] as backbone and with arabinan, galactan, and arabinogalactan at the O-4 position of the rhamnose residues (Tian et al. 2017). In the human intestine, pectins are fermented by the resident microbiota including the genera related with anti-inflammatory effects (Onumpai et al. 2011). Pectin fermentation also brings the production of SCFAs. It increases bacterial species belonging to *Clostridium* cluster XIV (*Lachnospira, Dorea,* and *Clostridium*), which results the increase of butyrate levels (Bang et al. 2018). Moreover, pectins with different structures show changes in fermentation characteristics. The low-methyl esterified pectin is fermented more efficient than high-methyl esterified pectin in the cecum and consequently results in a higher production of SCFAs, propionate and butyrate (Tian et al. 2016). As a prospective approach, *in vitro* fermentation of citrus pectin in combination with *Bifidobacterium longum* can modulate the obesity-related microbiota, and this treatment stimulated members of the Ruminococcaceae and Succinivibrionaceae families, resulting an increase in butyric and acetic acids (Bianchi et al. 2018).

Water-soluble alkaline polysaccharides

Water-soluble alkaline polysaccharides are not so common as neutral and acid polysaccharides in the nature. Chitin, the main component of the exoskeleton of marine crustaceans (Yen, Yang, and Mau 2009), is a water-insoluble polysaccharide composed of a linear β-1,4-linked polymer of N-acetylglucosamine (Shahidi, Arachchi, and Jeon 1999). In contrast, chitosan is the product of partial or full deacetylation of chitin, and is the unique alkaline polysaccharide in the nature (Cheung et al. 2015). Both chitin and chitosan are resistant to digestive enzymes in human and animals (Ringø et al. 2012; Xiao et al. 2016). Chitosan is a common ingredient in functional foods and cosmetics. One of its most important beneficial effects is regulation of the gut microbiota and intestinal ecology (Vernazza, Gibson, and Rastall 2005). Both chitosan and its oligosaccharides show the potential to promote the growth of fecal microbiota and even the production of SCFAs. Similar to other NDCs, chitosan oligosaccharides show better effects on the production of SCFAs than the higher molecular weight fractions. *In vitro* tests have shown that chitosan oligosaccharides (DP 2–8) stimulate the growth of *Lactobacillus brevis*, *Lactobacillus casei*, and *Bifidobacterium bifidium* (Lee et al. 2002). Chitosan oligosaccharides even show prebiotic effects comparable to those of traditional prebiotics, such as inulin and lactose, on the growth of *Bif. bifidium* and *Bifidobacterium breve*, demonstrating that chitosan oligosaccharides may have applications as novel prebiotics (Nurhayati et al. 2016). However, some *in vivo* studies have shown conflicting results. For example, Mateos-Aparicio et al. (2016) demonstrated that acetylated chitosans and their oligosaccharides are not potential prebiotics. Additionally, Mrázek et al. (2010) showed that chitosan intake did not influence the abundance of beneficial microbes, including butyrate-producing bacteria and *Bifidobacterium* spp. Koppová et al. (2012) also found that chitosan and its oligosaccharides had no prebiotic effects on the growth of *Bifidobacterium* spp. in the gastrointestinal tract of Wistar rats. Thus, further studies are needed to elucidate the prebiotic applications of chitosan and its oligosaccharides.

Other nondigestible oligosaccharides (NDOs) and their derivatives

Various other NDOs and their derivatives also exhibit potential prebiotic activity. These compounds contain isomalt-oligosaccharides (IMOs), galacto-oligosaccharides (GOSs), XOSs, and some pseudo-oligosaccharides, such as acarbose. Soybean oligosaccharides are another important commercial NDOs and are extracted directly without enzymatic manufacturing processes from soybean whey, with raffinose, stachyose, and verbascose as the main components (Karr-Lilienthal et al. 2005; Mussatto and Mancilha 2007). Oligosaccharides are typically defined as saccharides containing between 3 and 10 sugar moieties. However, some disaccharides possess properties similar to those of oligosaccharides, such as lactulose and xylobiose (Vázquez et al. 2000). Therefore, the NDOs described in this section include common oligosaccharides and disaccharides with prebiotic activity.

GOSs are some of the most abundant oligosaccharides in human breast milk and are important for early establishment of the intestinal microbiota in babies. GOSs can be utilized by *Lactobacillus* and *Bifidobacterium* spp. (Watson et al. 2013). Additionally, GOS supplementation resulted a 100-fold increase in the abundance of *Bifidobacterium*, accompanied by a smaller increase in the abundance of the butyrate-producing bacterium *F. prausnitzii* (Davis et al. 2011). Several reports have also shown that GOS supplementation mixed with inulin/FOS increases the abundance of *F. prausnitzii* in human volunteers (Dewulf et al. 2013; Ramirez-Farias et al. 2009), which may contribute to the production of butyrate.

Isomalt is an equimolar mixture of two mutually diastereomeric disaccharides, α-D-glucopyranosido-1,6-mannitol and α-D-glucopyranosido-1,6-sorbitol (Bolhuis, Engelhart, and Eissens 2009). It is slowly and only partly digested and absorbed in the upper gastrointestinal tract (Langkilde et al. 1994). Undigested and unabsorbed portions reach the colon and are fermented completely by the gut microflora. *Bifidobacterium* can utilize isomalt as the sole carbohydrate source. IMO is mixture that contains isomaltose (O-α-D-glucopyranosyl-(1-6)-D-glucopyranose), panose, isomaltotriose, and several other branched oligosaccharides composed of four or five glucose residues. Dietary IMOs have been reported to increase cecal concentration of SCFAs (Djouzi and Andrieux 1997), particularly butyrate and iso-butyrate levels in the jejunum (Zhang et al. 2003).

Similar to GOS, lactulose is also manufactured from lactose. Lactulose is a synthetic disaccharide (galactofructose) produced by alkali isomerization, which converts the glucose moiety of lactose to a fructose residue (Villamiel et al. 2002). At low doses, lactulose increases the numbers of *Bifidobacterium* and *Lactobacillus* cells while reducing the numbers of harmful *Salmonella* spp. and *E. coli* in the gastrointestinal tract (Krueger et al. 2002; Schumann 2002). Inclusion of lactulose and *Lactobacillus plantarum* in the diet significantly improves the performance and colonic microbial activity of weaning piglets (Guerra-Ordaz et al. 2013). The treatment also increases the number of total *Lactobacillus* cells and the percentage of butyrate in the colon, demonstrating a potential symbiotic relationship.

The α-glucosidase inhibitor acarbose, a pseudo-oligosaccharide, is used as antidiabetic drug to treat diabetes mellitus type 2 (Wolever and Chiasson 2000). It inhibits glycoside hydrolases in the small intestine, thereby reducing the digestion rate of starch and promoting the entry of starch into the colon for fermentation, thus, obviously increasing the concentration of butyrate in the colon (Weaver et al. 1992). The entry of starch into the colon results the increased growth of starch-fermenting butyrate-producing bacteria (Weaver et al. 1997). Wolever and Chiasson (2000) also found an increase of serum butyrate after 4 months administration of acarbose, speculating that a small proportion of colonic butyrate may reach peripheral blood and exert its physiological functions.

In addition to the NDCs introduced above, some monosaccharide derivatives, including gluconic acid and sorbitol, have also been shown to have butyrate production ability. *Lactobacillus* species are thought to be the major gluconic acid utilizer, and during fermentation, the product lactate is efficiently converted to butyrate by *M. elsdenii* (Tsukahara et al. 2002). Sorbitol can also improve the production of propionate and butyrate in some *in vitro* fermentation models (Kiriyama, Hariu, and Sakata 1992).

Factors affecting butyrate production

The physical and chemical properties of NDCs are related to their metabolism by the gastrointestinal microbiota, which are involved in fermentation and therefore alter microbial diversity and SCFA production in the colon (Brahe, Astrup, and Larsen 2013; Klosterbuer et al. 2013; Bindels, Walter, and Ramer-Tait 2015). NDCs provide major substrates for microbiota fermentation in human intestinal tract, however, only a few NDCs are butyrogenic. Dietary strategies, including selection of specific NDCs, have been studied to optimize butyrate production and improve colonic health. Carbohydrate composition and structure varies in different types of NDCs, thus give rise to different amounts and patterns of butyrate during *in vivo* and *in vitro* microbiota fermentation, possibly by modulating the metabolic pathways of bacteria. Butyrogenic effects are likely to be influenced by features of NDCs, including the solubility, the monomeric carbohydrate composition, the distribution of chain lengths, branching and substituents (Karppinen et al. 2000; Henningsson, Björck, and Nyman 2002; Nilsson and Nyman 2005). Moreover, the gut environment and major inter-individual variations in microbiota composition also influence bacterial metabolism and competition, and thus affect butyrate fermentation (Louis et al. 2010)

Solubility

The solubility of carbohydrates is likely to affect the fermentability of NDCs significantly and results in cross-feeding among different groups of bacteria. Much dietary NDCs enters the gut in the form of insoluble particles, which requires specialized bacteria for the process of degradation (Flint et al. 2008). The insoluble NDCs (e.g., wheat bran and cellulose) are usually associated with decreased colonic transit time and increased fecal mass (Tungland and Meyer 2002). They are generally more resistant to colonic fermentation than soluble NDCs (Jenkins and Kendall 2000), with a slower fermentation rate and higher butyrate levels in the distal colon (McIntyre, Gibson, and Young 1993). The soluble NDCs are generally highly fermentable and thus can be used quickly by microbes (Rose et al. 2007). The fermentation in the colon results the production of SCFAs and physiologically active by-products (Anderson et al. 2009). *In vitro* studies have also demonstrated a linear association between the amount of soluble NDCs and the production of SCFAs (Mortensen and Nordgaard-Andersen 1993). Therefore, the soluble NDCs can function as prebiotics for modulating the structure and metabolism of the gut microbiota and can influence intestinal health by affecting other intestinal characteristics, such as changing the bile acid profiles and lowering the pH in the lumen. Additionally, the viscosity of these NDCs result in an extended feeling of fullness and delays gastric emptying (Lockyer and Nugent 2017). However, rapidly fermented NDCs, commonly fermented in the cecum and proximal colon, may not provide as much SCFAs to the distal colon as slowly fermented NDCs (McIntyre, Gibson, and Young 1993).

Arabinoxylans (AXs), the main DF in grains of wheat and related cereals, show prebiotic and fermentation characteristics depending on their structural properties (Izydorczyk and Biliaderis 1995). As shown by Damen et al. (2011), the water unextractable AX-rich preparation was only partially fermented in the ceco-colon with increasing the levels of butyrate and the *Roseburia/E. rectale*. However, the consumption of a water-extracted AX-rich preparation increased acetate production and induced a selective bifidogenic response. Inulin, a soluble fermentable fiber, is quickly and easily fermented in the intestinal tract (Roberfroid 2007). During *in vitro* fermentation, inulin shows a faster fermentation speed and produces a higher molar ratio of butyrate after both 4 and 24 h of fermentation compared with cereal bran (Karppinen et al. 2000). In addition to the effects of SCFA patterns, insoluble NDCs, such as wheat bran, can decrease fecal bile acid concentrations compared with soluble psyllium fiber (Ejderhamn, Hedenborg, and Strandvik 1992). Therefore, the combination of both soluble and

insoluble NDCs may have complex and beneficial effects on host health.

Length of the chain

In addition to solubility, the length of the chain also affects patterns of SCFA production. NDCs with longer chain are commonly more resistant to intestinal fermentation with a slower utilization rate; thus, metabolism occurs more distally in the colon (van de Wiele et al. 2007). In contrast, NDCs with shorter chain are more accessible to the microflora and are commonly associated with rapidly increased production of SCFAs (Barry et al. 1995; Kleesen et al. 1997; van de Wiele et al. 2007).

NDCs with specific chain lengths affect the molar ratios and production patterns of SCFAs. For example, fermentation on undegraded guar gum shows that acetate is the major SCFA produced by fecal bacteria, followed by propionate (Khan and Edwards 2005; Velázquez et al. 2000). However, hydrolyzed guar gum molecules with molecular weights of 10 and 15 kDa, were reported to produce butyrate as the greatest proportion of SCFAs (Pylkas, Juneja, and Slavin 2005). OF, oligofructose with DP 2-8, shows the highest butyrate production in SCFAs, whereas long-chain inulin (average DP of 23) generates the highest level of propionate (Nilsson and Nyman 2005). In order to enhance the coefficient of utilization, oligosaccharides with short chain length are obtained from high polymer carbohydrates by enzymatic or chemical hydrolysis.

Furthermore, the distribution of chain lengths seems to affect the fermentation site by influencing the prebiotic and butyrogenic properties of NDCs. Inulin-type fructans with different degrees of polymer (DP) have been assessed with microbiota from the proximal and distal colon *in vitro* (van de Wiele et al. 2007). Both OF (DP 2–20) and inulin (DP 3–60) produce high level of butyrate and stimulate lactate-producing bacteria. However, treatment with inulin gives a slower fermentation rate than OF, which also induces butyrate production in the distal colon regions compared with OF treatment. NDCs with longer chain lengths are typically less (or more slowly) biodegradable than those with shorter chain lengths (Roberfroid, van Loo, and Gibson 1998). This will prolong the treatment period required to achieve prebiotic effects *in vitro* and *in vivo*. Additionally, a combination of short-chain and long-chain AXs is physiologically more active than the individual fractions (Damen et al. 2011).

Monomeric composition of NDCs

Most of the butyrate-producers are not preferential carbohydrate degraders; they are likely to use partial breakdown products as substrates, which are released by specialized primary degraders (e.g. bifidobacteria/lactobacilli/bacteroides) (Flint et al., 2012; Rogowski et al., 2015). Once monosaccharides are liberated from the main chain, they can be metabolized into Embden/Meyerhof/Parnas pathway intermediating for SCFA production. The monomeric composition of NDCs is involved in SCFA fermentation; however, the results of various studies have not been conclusive (Henningsson, Björck, and Nyman 2002).

Intestinal microorganisms employ hydrolyase during NDC fermentation to degrade carbohydrate molecules. For example, members of the genus *Bifidobacterium* can express intracellular β-fructofuranosidase to hydrolyze fructose moieties from the terminal β-2,1 position during fructan and sucrose hydrolysis (Ehrmann, Korakli, and Vogel 2003; McKellar and Modler 1989; Warchol et al. 2002). *B. ovatus* produces α-galactosidase and mannanase for guar degradation (Hartemink, Schoustra, and Rombouts 1999; Macfarlane et al. 1990). The metabolic patterns vary for different monosaccharides. Fructose can be metabolized to fructose-1-phosphate by fructokinase or ketohexokinase by bypassing the two highly regulated steps of glycolysis, i.e., glucokinase/hexokinase and phosphofructokinase catalysis (Khitan and Kim 2013). Besides, fermentation of mono- and disaccharides *in vitro* appears to favor selective SCFA formation. For example, butyrate production is increased during sorbitol fermentation, whereas glucose, xylose, and fructose selectively increase acetate production (Mortensen, Holtug, and Rasmussen 1988; Gietl et al. 2012). Xylose tends to have greater effects than glucose and uronic acids on butyrate production (Salvador et al. 1993), and lactose selectively increases acetate production (Gietl et al. 2012; Mortensen, Holtug, and Rasmussen 1988). In contrast, rhamnose selectively increases propionate production in both *in vivo* and *in vitro* fermentation (Vogt, Pencharz, and Wolever 2004; Vogt et al. 2004).

Most studies have been conducted using single substrates, treating the butyrate-producing species as a single entity to study changes in SCFA patterns and investigate separate biochemical events. *R. inulinivorans* produces butyrate and propionate from glucose and fucose, respectively, whereas *Coprococcus catus* produces butyrate from fructose and produces propionate from lactate (via the acrylate pathway) (Reichardt et al. 2018). *Cl. butyricum* TK2 and *Cl. butyricum* CB8 have been reported to degrade XOSs, GOSs, and IMOs. IMOs, glucose oligomers with α-D-(1,6)-linkages, produce higher levels of butyrate with these two strains than GOSs and XOSs. XOSs and GOSs are both linear chains of β-(1→4)-linked galactose and xylose, respectively; however, GOSs significantly promote cell proliferation and butyrate production for both two species compared with XOSs (Wang et al. 2014). XOSs are highly selective oligosaccharides for human colonic butyrate-producing bacteria and *Bifidobacterium* strains *in vivo*, whereas GOS metabolism is prevalent in these strains (Scott et al. 2014).

Butyrate formation varies according to the monomeric composition of NDCs *in vivo*. For example, during consumption in rats, two disaccharides with β-1,4-linkages, i.e., lactulose (galactose and fructose) and lactitol (galactose and glucitol), can reached the colon, where they are fermented (Nilsson and Nyman 2005). However, lactulose was shown to induce higher butyrate production in the cecal and distal colon than lactitol. Variations in the microbial composition may explain the increases in butyrate because lactulose has

been shown to selectively stimulate the number of *Bifidobacterium* cells in humans (Tuohy et al. 2002), whereas lactitol decreases *Bifidobacterium* and *Bacteroides* populations *in vitro* (Probert et al. 2004). The human diet contains mixtures of NDCs; thus, further research is needed to elucidate the possible synergistic/antagonistic effects of combining NDCs.

Orientation and position of the glycosidic bond

With the degradation of NDCs, the liberated monosaccharides can therefore be taken up for fermentation, and differences in the orientation and position of the glycosidic bond may affect the SCFA pattern. This has been evaluated with respect to oligodextrans (predominantly α-1-6 glucans), which are selectively metabolized, whereas maltodextrins (α-1-4 glucans) are not (Olano-Martin, Gibson, and Rastall 2002). In order to evaluate how the orientation and position of the glycosidic bond affects SCFA patterns, isomeric disaccharides are often chosen. In some *in vitro* fecal fermentations, disaccharide isomers containing α bonds have been shown to induce higher butyrate production than β-bonded isomers. Sanz et al. (2005) reported that diglucose α(1-1)α (α,α-trehalose) produces more butyrate than diglucose β(1-1)β (β,β-trehalose) and 3α-digalactose (3α-galactobiose). Harriset al. (2017) also demonstrated that α,α-D-trehalose fermentation leads to significantly higher butyrate production and a lower proportion of acetate than other α- and β-bonded diglucoses. The same tendency was observed with galactobiose; 3α-digalactose (3α-galactobiose) showed higher butyrogenic effects than 4β-galactobiose and 6β-galactobiose (Sanz, Gibson, and Rastall 2005). Moreover, different bond positions may also affect butyrate production. For example, after incubation with human feces, 4β-diglucose (D-cellobiose) produced the highest levels of butyrate compared with other β-bonded diglucoses (1-1, 1-2, 1-3, 1-5) (Harris, Edwards, and Morrison 2017), and 6α-mannobiose produced significantly higher levels of butyrate than 2α-mannobiose, 3α-mannobiose, and 4α-mannobiose (Sanz, Gibson, and Rastall 2005). The human diet contains various NDCs; thus, it is difficult to evaluate the contribution of bond position and configuration without confounding effects, such as solubility and DP of NDCs. Therefore, further studies are needed to explain the relationship between bond configuration and SCFA patterns.

pH

The intestinal environment may have a great impact on bacterial metabolism and competition. The pH of the gut lumen is likely to be a key factor in intestinal health, with a number of important physiological effects, such as alterations in the availability of cations and bile acid solubility (Scholz-Aherns and Schrezenmeir 2007). Moreover, pH can modulate microbial colonization in the upper gastrointestinal tract, particularly the acidic conditions of the stomach (Ohland and Jobin 2015). In the large intestine, variations in pH affect the microbial community composition and metabolic activity (Belenguer et al. 2007; Walker et al. 2005); for example, reduced pH can prevent the growth of pathogenic *E. coli* under simulated gut conditions (Flint et al. 2007).

Acid production is increased with the supplement of fermentable NDCs, thus leading to a decreased luminal pH, especially in the proximal colon. Butyrate formation has been shown to be affected not only by the proportion of butyrate-producing bacteria in the overall community but also by the pH (Reichardt et al. 2018). Changes in pH leads to differences in substrate preferences and competitive abilities of microbiota. Lowering of the gut pH may also contribute to the production of butyrate in human colonic bacterial community. As reported by Duncan et al. (2009), the tested butyrate-producing species grew well at pH 5.5, giving growth rates at least 50% of those at pH 6.7, whereas the all tested *Bacteroides* species grew poorly at pH 5.5. Afterwards, in the complex fecal fermentation, butyrate-producing *Roseburia/E. rectale* populations showed a competitive advantage to other groups, particularly *Bacteroides* spp., at pH 5.5 (Duncan et al. 2009). Within *in vitro* fecal fermentation conducted by Walker et al. (2005), pH 5.5 resulted in a higher butyrogenic fermentation and a decreased acetate and propionate concentration compared to pH 6.5. Besides, *Roseburia* spp. and *F. prausnitzii* express the butyryl-CoA: acetyl-CoA transferase pathway for butyrate formation, and the lower pH (5.5) favors higher acetate consumption and butyrate production per mol of carbohydrate consumed (Louis and Flint 2017). Thus, slightly acidic pH in gut environment is likely to confer a competitive advantage to groups of butyrate-producers for completing for substrates (Kettle et al. 2015; Walker et al., 2005).

Owing to the higher fermentation rate, the pH of the proximal colon is lower (5.5–6.5) than that of the distal colon (6.5–7.0) (Cummings and Macfarlane 1991). The lower pH is likely to promote butyrate formation in the proximal colon by stimulating butyrate-producing bacteria (Walker et al. 2005). However, most cases of colon cancer appear distally in humans and rodents with experimentally induced cancer (Bufill 1990; Holt et al. 1996). Thus, shifting the fermentation site to the distal part of the colon with a mixture of NDCs may be an effective strategy (Topping, Illman, and Trimble 1985).

Microbial distribution and variation in the gut

The intervention with dietary NDCs showed a modulating effect on SCFA concentrations, which was highly dependent on the initial characteristics of the intestinal microbial ecosystem (Ferrario et al. 2014). Advanced molecular and computational methods have revealed that the huge gastrointestinal microbial community plays a critical role in the normal development and function of the human body (O'Hara and Shanahan 2006; Sommer and Bäckhed 2013). Additionally, the microbiota diversity depends on the gastrointestinal site, with differences observed between the stomach, small bowel, cecum, colon, and rectum (Fig. 2). The bacterial composition of the stomach is dominated by *Propionibacterium*, *Lactobacillus*, *Streptococcus*, and *Staphylococcus*, with a density of around 10^2–10^4 CFU/g or CFU/mL (Delgado et al. 2013).

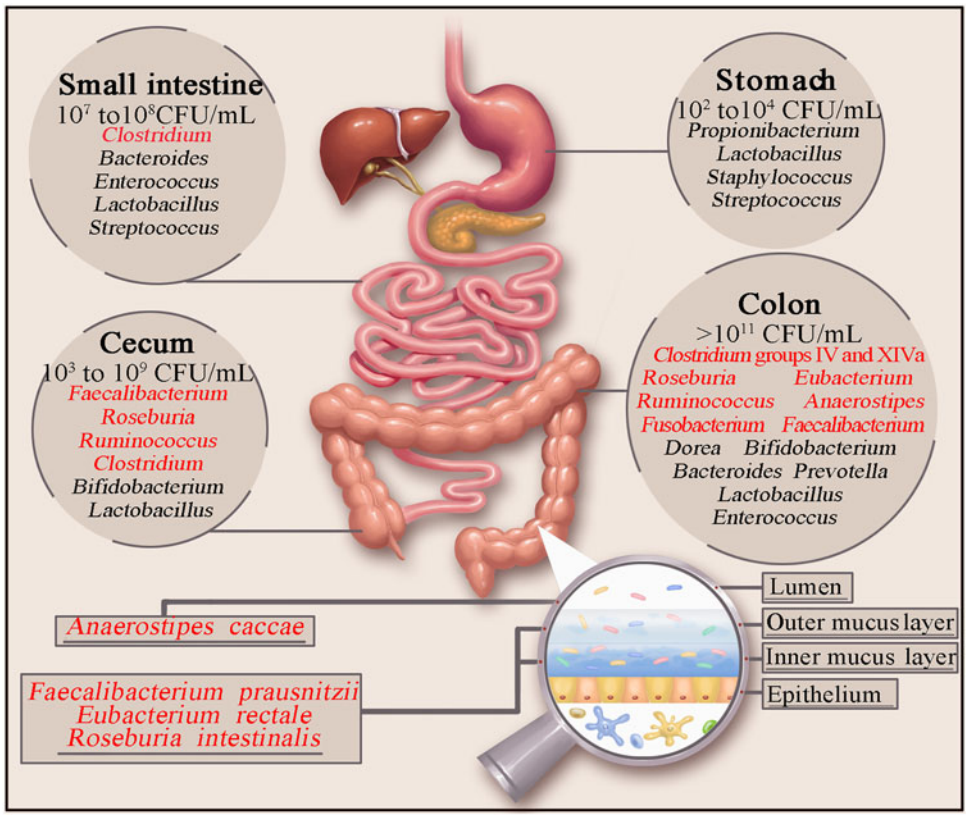

Figure 2. Distribution and abundance of butyrate producing bacteria in gastrointestinal tract of humans. The dominant SCFA producing bacteria in the stomach, small intestine, cecum, and colon are listed (Delgado et al. 2013; Jandhyala et al. 2015; Sartor 2008; Simon and Gorbach 1995; Tuohy and Scott 2015; Zoetendal et al. 2012; Jandhyala et al. 2015; Sartor 2008; Tuohy and Scott 2015). Butyrate producers with different colonizing locations are marked in red. The bacteria *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Roseburia intestinalis* predominantly colonize the mucus layer, whereas *A. caccae* mainly colonizes the lumen of the colon (van den Abbeele et al. 2013; El Aidy et al. 2013).

In contrast, *Streptococcus* sp., *E. coli*, *Clostridium* sp., and other organisms with high G + C content are most abundant in the small intestine (Zoetendal et al. 2012). The ecological conditions in the cecum differ from those in the distal colon (based on fecal samples). *Bacteroides*, *Porphyromonas*, *Prevotella* spp., and *Clostridium* groups represent 44% of fecal bacterial rRNA, whereas rRNA from *E. coli* and the *Lactobacillus-Enterococcus* group represents 50% of cecal bacterial rRNA (Marteau et al. 2001). The bacterial density in the upper gastrointestinal tract (10^5 CFU/mL in the jejunum and 10^6 CFU/mL in the ileum) is low compared with that in the cecum (10^8 CFU/mL) and feces (10^{10} CFU/mL) (Marteau et al. 2001; Simon and Gorbach 1995). Moreover, the highest density is usually observed in colon and may exceed 10^{11} CFU/g or CFU/mL (Delgado et al. 2013).

Among gram-positive anaerobic bacteria, butyrate-producing bacteria are widely distributed in the colon. However, variations in bacterial colonization induce changes in gut epithelial homeostasis, further affecting host function (El Aidy et al. 2013). Microbial profiling during the establishment of microbiota-accommodating homeostasis has been conducted in the large intestine of ex-germ-free mice; the data indicated that butyrate-producing bacteria, which belong to *Clostridium* clusters IV and XIVa, are the main members of the group of stable, highly diverse, late colonizers. However, *Bifidobacterium* populations directly colonize the colon in high quantities after birth (Miquel et al. 2014). The butyrate-producing bacteria *F. prausnitzii*, *E. rectale*, and *R. intestinalis* predominantly colonize the mucus layer and consequently enhance the utility of butyrate by colon epithelial cells, whereas other species, such as *A. caccae*, preferentially colonize the lumen of the colon (van den Abbeele et al. 2013; El Aidy et al. 2013). Decreased populations of *Clostridium* clusters IV and XIVa have been observed in the elderly (Claesson et al. 2011); this difference may be related to decreased mucus production, which affects the habitat and fitness of mucosal butyrate producers (Collado et al. 2007).

Increasing evidence indicates that composition of the gut microbiota shifts with the changes of the diet. Inter-individual variations in microbial composition can strongly influence the responses to NDCs, including the degradation level of NDCs and the production of butyrate (Walker et al. 2011; Flint et al. 2007). However, based on the 16S rRNA DGGE and sequences profiling, many of the dominant phylotypes of gut bacteria show a degree of stability between individuals. According to the intestinal microbiota variation, three discrete enterotypes are classified across the healthy human population (Zoetendal, Akkermans, and De Vos 1998; Arumugam et al. 2011). Most of the reported *in vivo* tests explain the metabolism process of NDCs only under the fermentation of isolated bacteria and provide preliminary indication of the substrate as prebiotics. However, the ecosystem *in vivo* is complex and full of interspecies competition and cooperation (Flint et al. 2007). In order to evaluate the butyrogenic effects of NDCs, further research is

required to analyze the microbial ecology and systems, in particular, to evaluate the complex metabolic shifts and interactions under *in vivo* conditions.

Strategies for butyrate production

Because of the potential benefits of increasing butyrate levels in the gastrointestinal tract, more alternative approaches are being developed to deliver butyrate to the gastrointestinal tract, particularly the colon, for treatment of gut diseases (Hamer et al. 2008). However, butyrate can be absorbed in the small intestine; thus, orally administered butyrate may not all reach the large intestine (Scheppach et al. 1992). Butyrate enema can also be used as an effective therapy for treating colon or rectum diseases (Steinhart, Brzezinski, and Baker 1994).

In addition to exogenous butyrate supplements, alternative treatments can also contribute to increase colonic butyrate concentrations via endogenous generation mechanisms. NDCs are a good butyrogenic source for endogenous production of butyrate, and as discussed above, the amount of butyrate formed may depend on the structural properties of the NDCs. Moreover, consumption of several types of butyrate-producing probiotic bacterial strains, such as *Cl. butyricu*m and *B. fibrisolvens*, has been applied to deliver butyrate to the distal colon (Araki, Fujiyama, et al. 2000; Ohkawara et al. 2005). Furthermore, enhanced butyrate formation by cross-feeding between butyrate-producing bacteria and other colon bacteria has been given much attention.

Metabolic cross-feeding

Much dietary carbohydrate enters the large intestine in the form of insoluble fragments or soluble polymers, which may be utilized by specialized primary degraders. Specialized groups of microorganisms can be stimulated by treatment with NDCs, which possess enzymes showing carbohydrate degradation activity during fermentation. Metabolic products generated during the degradation of NDCs may then provide substrates to support secondary degraders; which is usually named as cross-feeding (Flint et al. 2012). These interactions include hydrogen transfer, and reutilization of fermentation products such as acetate and lactate, and of breakdown fractions released from complex polymers (Flint et al. 2007). Therefore, metabolic activities are greatly dependent on the mutualistic symbiosis and competitive fitness between the intestinal microbes (Reichardt et al. 2018). In fact, most NDCs have been observed to improve butyrate production via stimulating the cross-feeding between primary degrader (bifidobacterial/lactobacilli/bacteroides, etc.) and butyrate-producing bacteria while only few NDCs can function as a substrate for butyrate producers (Flint et al. 2008). Different types of NDCs can influence the population and the activity of the primary degrader, which can subsequently affect the fermentation by the secondary degraders and ultimately the formation of butyrate.

The substrate preference of the secondary fermenter contributes a lot to the diversity of cross-feeding interactions in the intestinal microbiota. Secondary degraders are likely to reutilize NDC breakdown intermediates (e.g., oligo-, mono-, and polysaccharides) released by primary degraders during fermentation. For example, *Roseburia* sp. utilize the partial breakdown products of NDCs released by *Bif. adolescentis* (Belenguer et al. 2006). Besides, the keystone starch degrader *R. bromii* can promote the growth of *A. hadrus*, a butyrate-producing, nonstarch utilizer, through the provision of starch breakdown products (Ze et al. 2013). This cross-feeding mechanism is also typically described between lactate- and acetate-producing and butyrate-producing bacteria. Several research works have reported the interaction between members of the genus *Bifidobacterium* and butyrate-producing bacteria, such as *Megasphaera*, *Roseburia*, *Eubacterium*, *Anaerostipes*, and *Faecalibacterium* (Belenguer et al. 2006; Falony et al. 2006; Rios-Covian et al. 2015; Tsukahara et al. 2002). Lactate and acetate, the fermentation end-products of bifidobacteria, can both boost butyrate formation. Butyrogenic bacteria *Roseburia and F. prausnitzii* are net consumers of acetate, which they require for optimal growth. Acetate can be used as a co-substrate to support butyrate formation via butyryl-CoA: acetyl-CoA transferase (Duncan et al. 2002). The co-culture experiment revealed that the formation of butyrate by *F. prausnitzii* was enhanced in the presence of *Bifidobacterium* (Rios-Covian et al. 2015). Additionally, lactate is always regarded as one of the most important metabolites from the fermentation of prebiotics by bifidobacteria and lactic acid bacteria and it can be utilized by other species including butyrate-producing bacteria and generally does not accumulate in healthy subjects (Koh et al. 2016). During co-culture, lactate produced by *Bif. adolescentis* provides substrates for *E. hallii* to synthesize butyrate via cross-feeding. Besides, many of butyrogenic *Roseburia* and *F. prausnitzii* are also hydrogen-producers, which can convert hydrogen into acetate when in co-culture with an acetogen, and subsequently promotes the growth of butyrate-producing bacteria (Chassard and Bernalier-Donadille, 2006). Overall, it can be seen that cross-feeding is a complex process depending on the coordination of intestinal microbiota and even the supplement of NDCs, which promote different groups of intestinal bacteria. The coordination between complex polymer degraders and secondary degraders is beneficial for the fast degradation and utilization of NDCs with different structures, and that coordination between lactate-, acetate- and butyrate-producing bacteria is important for the maximum production of butyrate.

However, the butyrate-producing bacteria require strict anaerobic conditions, which limits their practical application as probiotics (Immerseel et al. 2010). Instead of direct administration of butyrate-producing bacteria, attempts could be made to provide butyrate-producing substrate, such as lactate and acetate. Therefore, LABs could be useful probiotics for their property of indirect stimulation of butyrate production based on cross-feeding mechanism. Overall, the rational application of cross-feeding strategies for exogenous butyrate supplementation in the human colon is promising. However, further research on the intestinal

microbiota is necessary to effectively exploit the capacity of this strategy.

Combination of NDCs based on fermentation status

One of the most important functions for butyrogenic NDCs treatment is increased colonic persistence. However, as we discussed above, the composition and structure of NDCs are the factors which can influence butyrate production, besides the fermentation status. NDCs, such as guar gum, pectin, and oat bran, delivered to the cecum and proximal colon can be rapidly and fully fermented, leading to a bacterial proliferation with an increase in intestinal homeostasis, however, contributing less butyrate to the distal colon (McIntyre et al. 1991; Rose et al. 2007). This may also be true for RSs, which have a relatively rapid fermentation rate and are present with relatively high levels of cecal butyrate in rat models. Thus, the directional accumulation of colonic butyrate can be employed effectively for the human intestinal health, and various strategies are available to enhance butyrate levels in the distal colonic regions, where tumors most commonly occur.

Insoluble NDCs are generally more resistant to colonic fermentation than soluble NDCs, commonly have slower fermentation rates, and are associated with higher butyrate levels in the distal colon (Jenkins and Kendall 2000; McIntyre, Gibson, and Young 1993). Psyllium polysaccharide is slowly fermented in the colon, and more than 50% of that is devoid of bacterial degradation and is excreted into feces (Edwards et al. 1992). Following *in vivo* consumption in rats, the majority of water-extractable cereal AX and its oligosaccharides are fermented in the cecum with a selective bifidogenic response. In contrast, water unextractable AX is primarily fermented in the colon and increases the levels of butyrate and butyrate-producing *Roseburia/E. rectale* (Damen et al. 2011). Wheat bran is also slowly fermented, strongly enriching *E. xylanophilum* and *Butyrivibrio* spp., and providing higher amounts of butyrate in the distal colon than oat bran (Duncan et al. 2016; Reddy et al. 2000). The utilization of NDCs with longer chain lengths typically occurs more distally in the colon than that of NDCs with shorter chain lengths (Roberfroid, van Loo, and Gibson 1998; van de Wiele et al. 2007). The metabolism of short-chain NDCs commonly occurs in the cecum and proximal colon via stimulation of lactate-producing bacteria, such as *Lactobacillus* and *Bifidobacterium* (Damen et al. 2011; van de Wiele et al. 2007). Inulin with higher DPs is more resistant to saccharolytic fermentation; thus, metabolism occurs more distally in the colon, with enhanced butyrate levels. OF molecules having a relatively short chain length can be rapidly fermented, suggesting that the fermentation site for this molecule may be more proximal, likely toward the cecum (van de Wiele et al. 2007). Thus, the rational application of NDCs with particular fermentability which mainly depends on their water-solubility and molecular weights, may be effective to shift the fermentation site and to enhance butyrate levels in the distal colon.

Furthermore, interactions of NDCs with different characteristics can produce more complex and comprehensive effects on the butyrate fermentation status. For example, soluble and insoluble cereal AXs and its oligosaccharides together exert selective bifidogenic effects in the colon, inducing elevated levels of butyrate and butyrate-producing *Roseburia/E. rectale* (Izydorczyk and Biliaderis 1995). Since molecules with specific molecular weights show different SCFA production patterns, the combination of several molecules with different molecular weights could provide a more comprehensive treatment for modulation of the microbiota (Pylkas, Juneja, and Slavin 2005). Although NDCs with slow fermentation rates are good sources for colonic and cecal butyrate, longer times are required to achieve prebiotic effects. Therefore, combinations of NDCs may be a more comprehensive strategy to modulate the site of butyrate release in the gut, as has been evaluated by analysis of the combination of wheat bran and high amylose cornstarch; the findings suggested that incorporation of wheat bran delayed the site of fermentation of high amylose cornstarch to the distal part of the hindgut (Henningsson, Björck, and Nyman 2002). Thus, the directional accumulation of colonic butyrate based on the combination of NDCs with different fermentation status is an effective strategy for the human colonic health.

Synbiotics with different combinations

Synbiotics refer to synergistic combinations of prebiotics and probiotics that beneficially affect the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract (Pandey, Naik, and Vakil 2015). Most of the studied synbiotic approaches focus on the well-characterized probiotics, bifidobacteria and lactic acid bacteria. As a therapeutic strategy, synbiotics have the potential to enhance the survival of the introduced probiotics in the human gut (Gurry 2017). For example, the synbiotic administration of the genera *Bifidobacterium* and *Lactobacillus* with FOSs increases the proliferation of these microbes in the gut (Kaplan and Hutkins 2000). Feeding of lactulose and *L. plantarum* can significantly improve the performance and colonic microbial activity (Guerra-Ordaz et al. 2013). This treatment also increases the percentage of butyrate in the colon, since the metabolism of *Bifidobacterium* and *Lactobacillus* provides substrates to benefit the growth of butyrate-producing bacteria. Synbiotic therapies focusing on butyrate-prodution have the potential to benefit human health in a variety of gut diseases (Card, Hubbard, and Logan 2003). In fact, synbiotics with different combinations bring us multiple options for achieving maximum production of butyrate in the intestinal environment. However, research on synbiotic therapies combining butyrate-producing probiotics with their fermentation substrates is lacking.

Moreover, NDCs that can be easily fermented into lactate or acetate, serving as substrates for lactate- and acetate-utilizing bacteria colonization. Benefiting from the metabolic products of NDCs, the population of butyrate-producing bacteria in the intestinal tract is subsequently increased. For example, *in vitro* fermentation of citrus pectin in combination with *Bif. longum* stimulates the members of the

Ruminococcaceae and Succinivibrionaceae families, resulted an increase in butyrate (Bianchi et al. 2018). Novel synbiotic strategies can be put forward depending on well understanding of the intestinal ecology and cross-feeding relationships. Therefore, a butyrate-producing synbiotic approach can be constructed with the combination of a lactate-utilizing butyrate producer such as *E. hallii* or *A. caccae*, a lactate producer such as bifidobacteria, and a prebiotic that is easily fermented into lactate. Besides, administration of multiple prebiotics promoting both butyrate producer and acetate producer can be adopted to accelerate the accumulation of butyrate in the intestinal tract. Therefore, to realize a maximum production of butyrate based on the synbiotic approach, the combination of more than a simple pair of probiotic and an associated prebiotic is needed.

Stimulating endogenous butyrate production in order to improve gut health is discussed in this review. This can be achieved by using butyrogenic NDCs that stimulate the proliferation and the metabolic activities of the butyrate producers. Additionally, supplements with butyrogenic bacteria or synbiotics are an alternative strategy. However, obvious inter-individual variation in the composition of the gut microbiota significantly affects the individual response to NDCs. Moreover, the gut environment is complex and variable, depending on the metabolism of colonized microbiota, dietary composition, the inhibitors and promoters excreted by the intestinal tissue, and various physicochemical factors including osmolarity and pH (Flint et al. 2007; Louis, Hold, and Flint 2014; Sonnenburg and Bäckhed 2016). Therefore, a range of systematic investigations are needed to analyze the specific effects of the different bacteria and NDCs that may play a potential role in gut health, in addition to various metabolites with unknown functions. The inter-individual variation and complex metabolic shifts and interactions must be given full consideration in the design of future therapies, especially under *in vivo* conditions.

Conclusion

Various NDCs including water-soluble and insoluble polysaccharides, oligosaccharides and few disaccharides, have been studied for their physiological functions such as promoting the production of SCFAs including butyrate, and the proliferation of butyrate-producing bacteria. Not all NDCs are equally butyrogenic. The physical and chemical properties of NDCs are related to the butyrate metabolism of gastrointestinal microbiota. These microorganisms ferment NDCs, and subsequently alter microbial diversity and butyrate production in the colon. The relationship between the precise structure of NDCs and its metabolism in the gut is not clear yet, however, it is believed that water-soluble and/or lower molecular weight NDCs (e.g., PHGG and OF) are commonly easily fermented in cecum and proximal colon, thus may not provide much SCFAs to the distal colon. Therefore, dietary strategies by combining specific NDCs are promising to optimize butyrate production and to improve colonic health.

As mentioned above, butyrate exhibits multiple effects including the inhibition of colonic carcinogenesis, the improvement of the colonic defense barrier function, the promotion of satiety, and reduction of inflammation and oxidative stress. However, the effects of increased butyrate production are accompanied by other effects of NDCs and its fermentation, such as promoting intestinal propelling and modifying the intestinal microbiota. The contribution of butyrate to human health depends on its concentration and site of production. However, it can sometimes show contrasting effects in obesity and other physiological response. The complexity of the situation indicates that more emphasis should be placed on human *in vivo* studies to elucidate the function of butyrate in health.

The contribution of bacteria in the intestinal tract is critical for butyrate metabolism. Several butyrate-producing microorganisms such as *F. prausnitzii*, *Anaerostipes*, *Eubacterium*, and *Roseburia* species have been identified. In addition to the above bacteria that can produce butyrate directly, some bacteria can also enhance butyrate production through cross-feeding interactions. For instance, *Bifidobacterium* species present within the human colon are mainly lactate and acetate producers. It is well known that lactate and acetate can act as precursors for butyrate synthesis, which may help modulate the accumulation of lactate and acetate in intestinal environment. It has been reported that the co-culture of *Eubacterium limosum* and *Bif. longum* led to lower lactate and higher butyrate production when compared to pure cultures. Research on cross-feeding interactions between acetate or lactate producers and butyrate producers will be helpful for the development of probiotics.

Synergistic combination of prebiotics and probiotics is potential beneficial for endogenous generation of butyrate. To promote the production of butyrate, synbiotic therapies combining butyrate-producing probiotics with their fermentation substrate NDCs have the potential to benefit intestinal health. Besides, lactate-/acetate-producing bacteria are also helpful for the construction of butyrate-producing synbiotics. Inclusion feed of lactulose and *L. plantarum* significantly increases the number of total lactobacilli and the percentage of butyrate in the colon. Synbiotic administration of *Bifidobacterium* and *Lactobacillus* with FOS also increases their proliferation in the gut. Therefore, a variety of NDCs promoting the proliferation of butyrate-producing and/or lactate-/acetate- producing bacteria can be adopted for the synbiotic administration to facilitate the accumulation of butyrate. Besides, the combination of NDCs with different fermentation status also can be an effective strategy for directional accumulation of colonic butyrate. However, better understanding of the complex mechanisms underlying butyrate fermentation, absorption, and action in intestinal physiology is still needed to facilitate the rational application of butyrate and its associated NDCs for improvement of gut health.

Funding

The authors are grateful for the financial support by the Key Research and Development Project Foundation of Shandong

Province (2017YYSP003) and Shandong Natural Science Fund (ZR2017MD006).

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