Prebiotics, FODMAPs and dietary fibre –conflicting concepts in development of functional food products?

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Abstract

The term prebiotic relates to beneficial modulation of intestinal microbiota by dietary carbohydrates, however, uncertainties of the differentiation of the term “prebiotics” from dietary fibre as well as FODMAPs impede development of functional foods containing prebiotics. This communication outlines similarities and differences between prebiotics, FODMAPs, and dietary fibre, focusing on three areas of recent advancement: (i) oligosaccharide digestion in the small intestine; (ii) conditional digestibility of dietary glycans and (iii) impact of the food matrix on carbohydrate digestion. Because of large inter-individual differences in carbohydrate digestion, one type of prebiotics does not fit all consumers. The use of a diversity of prebiotics and their use in diverse food applications can address negative consequences associated with the consumption of prebiotics.

Introduction

The diet and particularly dietary carbohydrates are recognized as key determinants for the composition and function of intestinal microbiota [1, 2]. The term “prebiotic” provides a widely recognized label for the concept of beneficial modulation of intestinal microbiota by dietary carbohydrates [3, 4]. Functional foods containing prebiotics have been a significant driver for growth and diversification in the functional food market [5]. Despite scientific validation of the prebiotic concept, however, uncertainties associated with the definition of the term “prebiotics” and its differentiation from the term dietary fibre impede development and marketing of functional foods containing prebiotics [3]. Moreover, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) contribute to the irritable bowel syndrome (IBS), resulting in the apparent paradox that addition or removal of the same compounds improves human health [6, 7]. This communication highlights recent developments related to prebiotics, FODMAPs, and dietary fibre to unravel similarities and differences between the concepts and the corresponding mechanisms.

Dietary fibre, prebiotics, and FODMAPS: definitions. The Codex Alimentarius defines fibre as carbohydrate polymers with ten or more monomers, which are not hydrolysed by enzymes in the small intestine of humans. Purified and synthetic carbohydrates are included in the definition if they have a benefit to human health [8, 9]. This definition is used by regulatory agencies for approval of fibre-related health claims; oligosaccharides with a degree of polymerization of 3 or higher are often included in the definition of fibre [10, 11, 12].

FODMAPs include monosaccharides, disaccharides, and oligosaccharides that escape absorption in small intestine [6]. The definition of FODMAPS includes diverse compounds that differ in their effect on intestinal microbiota and in their ability to elicit adverse intestinal symptoms;

50 dietary interventions and the development of low-FODMAP food products particularly aimed to
51 reduce the amount of fructose and inulin-type fructans in wheat and rye [7, 13].

52 Prebiotics are defined on the basis of functional rather than chemical properties. Regulatory
53 definitions of the term “prebiotic” or health claims for prebiotics have not been approved [11,
54 12]; the use of the term is based on scientific consensus. Prebiotics are defined as non-digestible
55 compounds that beneficially affect host health through microbial metabolism and modulation of
56 composition and/or activity of gut microbiota [4]. This definition restricts the prebiotic concept
57 to the intestine and omits the requirement for selective stimulation of specific microbiota, a
58 criterion that previously defined prebiotics [3, 4]. Current knowledge on carbohydrate
59 fermentation by intestinal microbiota, however, demonstrates that health benefits of dietary fibre
60 and prebiotics are not linked to selective stimulation of specific bacterial genera or species but
61 relate to the capacity of diverse members of intestinal microbiota for conversion of dietary
62 carbohydrates to health beneficial short chain fatty acids (SCFA) [10, 14, 15, 16]. Compounds
63 currently recognized as prebiotics are oligosaccharides or polysaccharides [3, 4, 12] and mostly
64 are also included in the definition of FODMAPs and dietary fibre. Some authors discussed health
65 effects of prebiotics and dietary fibre without differentiation between the terms [12] while others
66 argue to abandon the term ‘prebiotic” altogether [17]. The term prebiotics remains useful,
67 however, because it includes disaccharides that are not absorbed in the small intestinal but are
68 excluded from the dietary fibre definition. Moreover, the term is recognized not only by the
69 scientific community but also facilitates communication of health benefits of functional foods to
70 the general public [3, 10].

71 Table 1 lists prebiotics that are commercially available as food ingredients. Components of
72 commercial oligosaccharide preparations, particularly β-galactooligosaccharides (GOS) and

isomalto-oligosaccharides (IMO), contain significant proportions of carbohydrates that are hydrolysed in the small intestine (Table 1). The small intestinal digestibility of prebiotics relates to the production process and to the underestimated contribution of brush border glycosyl hydrolases to digestion of dietary carbohydrates [18].

Oligosaccharide digestion in the human intestinal tract.

Oligosaccharides are digested in the small intestine by pancreatic and membrane-bound brush border enzymes; large intestinal digestion of dietary glycans is mediated by intestinal microbiota and absorption of microbial fermentation products (Figure 1). Pancreatic amylases are specific for starch, brush border enzymes include maltase-glucoamylase, isomaltase-sucrase, trehalase, and β-glycosidase (lactase) [19, 20]. Brush border enzymes mediate (partial) hydrolysis of fructo-oligosaccharides (FOS), GOS and IMO (Table 1). Commercial GOS contain about 20% lactose [21, 22]; lactose, cellobiose, non-lactose disaccharides and trisaccharides are hydrolysed by brush border lactase [22, 23]. Isomaltose and linear α-(1→4) and or α-(1→6) trisaccharides in commercial IMO are hydrolysed by brush border maltase-glucoamylase and isomaltase-sucrase [24, 25]. The activity of brush border enzymes is variable between individuals and thus contributes to the inter-individual differences in oligosaccharide digestion [19]. Small intestinal digestion is complemented by microbial metabolism in the terminal ileum (Figure 1). Ileal microbiota are geared towards rapid intracellular metabolism of mono- and oligosaccharides [26, 27]. The inter-individual variability of ileal microbiota [26] also contributes to individual differences in the capacity for oligosaccharide digestion.

Conditional small intestinal digestibility of dietary carbohydrates

Starch. The rate of starch digestion is conditional on the starch source and reduced by physical accessibility of starch granules in intact plant cells, crystalline structures within starch, chemical

96 modification, or amylose-lipid complex formation [28, 29]. Microbial fermentation of resistant
97 starch modulates composition and activity of intestinal microbiota in a manner that is dependent
98 on the starch source and the individual composition of intestinal microbiota [30, 31, 32].
99 **GOS including lactose.** Brush border β-glycosidase (lactase), which mediates hydrolysis of
100 lactose and related oligosaccharides, is expressed by all human infants. Expression of brush
101 border lactase cedes in most children aged 5 - 10 years but lactase expression persists
102 approximately 25% of humans throughout adulthood [33]. The digestion of lactose and GOS is
103 thus conditional on the expression of intestinal lactase.
104 **Fructose.** Fructose is transported in the small intestine by GLUT5, which is specific for fructose,
105 and GLUT2, which alternatively transports fructose, glucose, or galactose [34, 35]. Fructose
106 transport is fastest when equimolar concentrations of glucose and fructose are present in the
107 intestinal lumen [35, 36]. The capacity of about 50% of healthy subjects was insufficient to
108 absorb a single bolus of 25 – 40 g fructose but the absorptive capacity of fructose is much lower
109 in some individuals [35, 36]. A high prevalence of fructose malabsorption, >80%, was observed
110 in IBS patients [37]. Non-absorbed fructose is rapidly fermented by ileal microbiota [36].
111 **FODMAPS versus prebiotics: Beneficial and adverse health effects.**
112 Carbohydrate digestion via microbial fermentation yields only 60 – 75% of metabolic energy
113 when compared to the absorption of monosaccharides in the small intestine (Table 2) [38].
114 Accounting for losses through fecal excretion of bacterial biomass and SCFA, Health Canada
115 and FDA estimate a caloric value of 2 kcal / g of dietary fibre [39]. Health effects of prebiotics
116 are derived from microbial production of SCFA [40, 41]. Table 2 provides an overview on health
117 benefits of prebiotics, and particular on the mechanisms underlying the beneficial of colonic
118 SCFA formation to human health. Butyrate is the preferred energy source by colonic epithelial

cells; excess butyrate and other SCFA are transported by the portal vein to the liver and peripheral organs [32], thus mediating systemic effects [42]. Recognition of SCFA by the G protein-coupled receptors GPR41, GPR43, and GPR109A [43, 44] also mediates systemic effects related to immunity and inflammation as well as satiety and glucose homeostasis (Table 2). Health effects that are specific for the carbohydrate structure include the prevention of pathogen adhesion, direct interaction with the immune system, and reduced cholesterol levels (Table 2). Although some prebiotics also mediate these effects, they are unrelated to microbial metabolism and prebiotic activity.

Adverse health effects of prebiotics relate to the accumulation of sugars in the small intestine, causing osmotic diarrhea [36, 45]. In addition, gas formation during rapid carbohydrate fermentation leads to abdominal pain and bloating [13, 46]. Structurally diverse oligosaccharides that are not absorbed in the small intestine equally result in adverse intestinal symptoms when a dose of 0.3 g / kg bodyweight is exceeded [38]. This value corresponds well to the dose of lactose, GOS or FOS that is tolerated without adverse symptoms (in lactose-intolerant subjects) [45, 47]. Prebiotics that are partially hydrolysed by brush border enzymes, particularly IMO and lactosucrose, are tolerated at higher doses [38]. The balance of adverse versus beneficial health effects is also dependent on the individual expression of brush border enzymes and the capacity of intestinal microbiota for carbohydrate fermentation. Intestinal microbiota adapt their fermentation capacity to the supply of dietary carbohydrates [47, 48]. Beneficial and adverse health effects related to intestinal oligosaccharide fermentation are thus two sides of the same coin and tolerance is highly variable between individuals and within an individual over time.

Dietary fibre versus prebiotics: Diet affects colonic fermentation of carbohydrates.

The consumption of fibre-rich whole grains foods is associated with a reduced risk of cardiovascular disease [49], type 2 diabetes [50], and colorectal cancer [51]. However, the effects of whole grain foods on gut microbiota and beneficial metabolites are depended on the fibre source and individual dietary habits [52, 53]. Most prebiotics are included in the Codex Alimentarius definition of dietary fibre; however, when referring to the initial definition of dietary fibre as "nondigestible carbohydrates and lignin that are intrinsic and intact in plants" [8], health effects of prebiotics and dietary fibre differ in three major aspects: (i) Plant cell wall carbohydrates consist of complex polysaccharides and fermented at a rate that avoids negative health effects of FODMAPS [11]; (ii) Whole grains comprise diverse polysaccharides, which contribute to an increase of intestinal microbial diversity and the resilience of intestinal microbiota to perturbation [52, 54, 55, 56,]; (iii) Plant cell wall carbohydrates are associated with phenolic compounds. Food phenolics influence carbohydrate digestion and intestinal microbiota (Figure 2) and thus modulate health benefits derived from dietary fibre or prebiotics. Accordingly, health effects of prebiotics are strongly dependent on the background diet including the presence of phenolic compounds [57, 58]. Supplementation of a chemically defined diet and a conventional rat chow with FOS in a rodent model of inflammatory bowel disease yielded divergent effects of the prebiotic on intestinal inflammation [59]. The health benefits of prebiotics are thus enhanced when they are consumed in the context of a diet rich in other plant secondary metabolites.

Concluding remarks.

The diet in affluent countries is deficient in fibre-rich fruits, vegetables and whole grain products. This "fibre gap" has long term implications for public health. Although health benefits of purified prebiotic carbohydrates differ from those of dietary fibre that is intrinsic and intact in

plants, prebiotics have a well-established record in improving host health. Prebiotics are thus a valuable tool in food development to address the "fibre gap" and to improve health aspects of processed foods. Owing to the conditional digestibility of many prebiotic carbohydrates and the inter-individual differences in carbohydrate digestion, one "size" of prebiotics does not fit all consumers. The use of diverse prebiotic compounds and their use food applications that include health beneficial plant secondary metabolites will address negative consequences associated with the consumption of fermentable disaccharides and oligosaccharides.

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Figure legends.

Figure 1. Overview on carbohydrate metabolism by intestinal microbiota. Dietary di- and trisaccharides are hydrolysed by brush border enzymes in the ileum, or metabolited by ileal microbiota, which are geared towards rapid intracellular metabolism of simple carbohydrates. Metabolites of ileal microbiota, particularly lactate, succinate, 1,2-propanediol, and acetate are intermediates of intestinal bacterial metabolism and further converted to butyrate or acetate by colonic microbiota. Purified non-starch polysaccharides are metabolized by extracellular enzymes of colonic microbiota but typically do not necessarily require microbial consortia for complete conversion to short chain fatty acids. Complex plant cell wall polysaccharides are partially or completely fermented by colonic microbiota. Fermentation of plant cell wall polysaccharide typically involves multiple microbial species and often involved solid state fermentation of plant cell wall particles. [12, 14, 26, 27, 76, 77]

Figure 2. Influence of phenolic compounds on carbohydrate digestion. **Left panel**. Phenolic compounds, particularly hydrolysable and condensed tannins, inhibit small intestinal glycosyl hydrolases and shift starch digestion from small intestinal absorption to colonic fermentation. **Middle panel.** Some phenolic compounds including tannins and phenolic acids have highly selective antimicrobial activity against members of intestinal microbiota. **Right panel.** Covalent and non-covalent crosslinking of cell-wall polysaccharides with phenolic acids decreases the rate of colonic fermentation. Drawn with information from [2, 11, 78, 79, 80, 81, 82, 83]

Table 1. Overview on composition, production methods, and digestibility of commercially available prebiotics for use in functional food products.

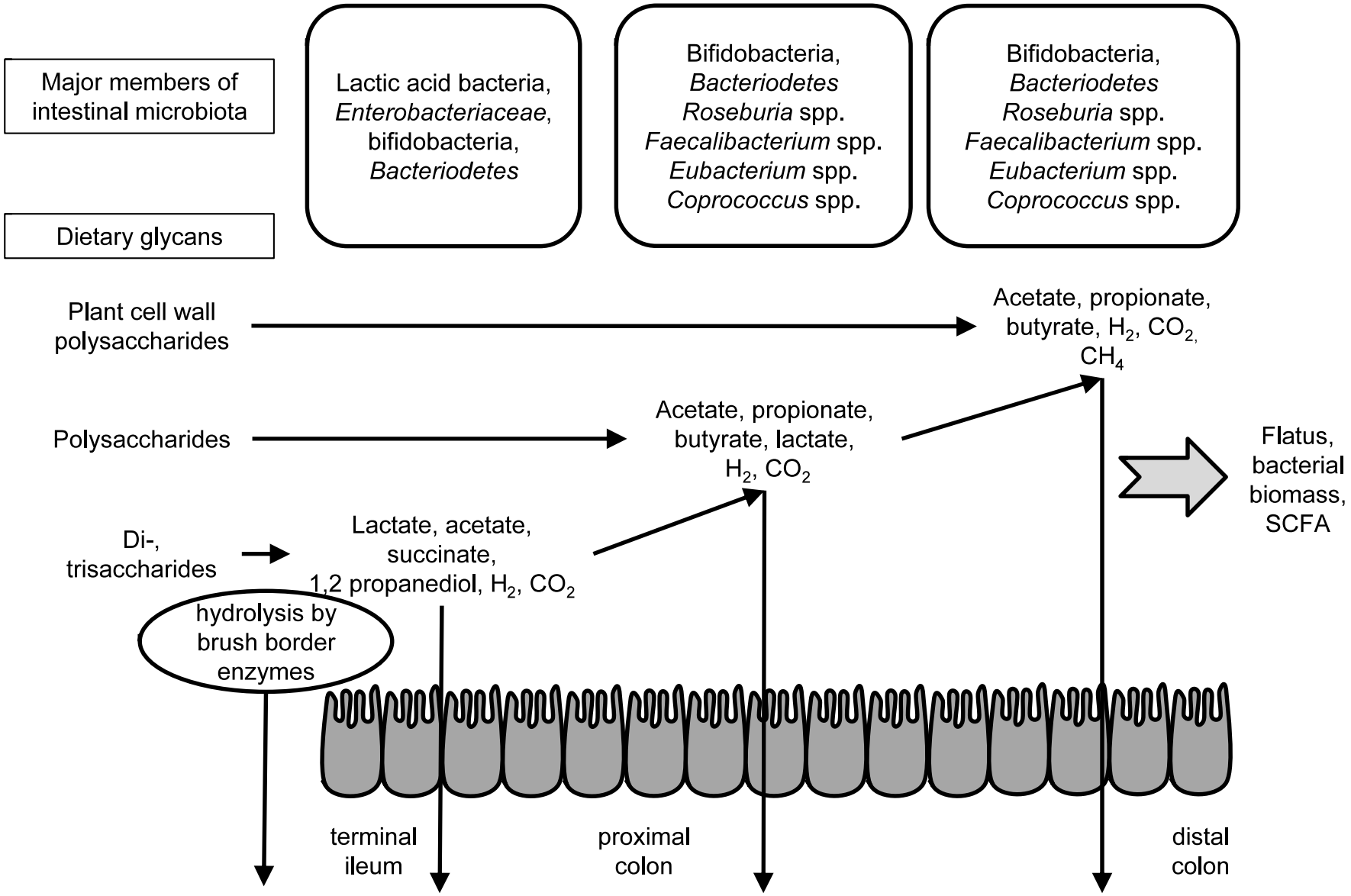
Prebiotic	Production method	Main linkage types	Main DP	Small intestinal digestibility	Ref
FOS, inulin	transglycosylation of sucrose or inulin hydrolysis	β(2→1), β(2→6)	3-60	12%[a)], 0%	[22]
Raffinose, verbascose, stachyose	Extraction from pulses	α(1→6), β(2→1)	3-5	0 %	[25]
Lactosucrose	transglycosylation of lactose or sucrose	β(1→4), β(2→1)	3	> 10%[a)]	[19]
β-Galacto-oligosaccharides	transglycosylation of lactose and galactose	β(1→4), β(1→6), β(1→3)	2-8	20-50%[a)]	[19]
Lactulose	chemical isomerization or transglycosylation of fructose	β(1→4), β(2→1)	2	> 10%[a)]	[21]
2-Fucosyllactose	Transgenic glycosyltranferases in *Escherichia coli*	α(1→2), β(1→4)	3	0 %	[58, 59]
Isomalto-oligosaccharides	transglucosylation of maltose with maltose as glucosyl donor	α(1→4), α(1→6)	2-4	40 – 70%[b)]	[24]
	transglucosylation of maltose with sucrose as glucosyl donor (panose-series oligosaccharides)	α(1→6), α(1→4),	3–10	20 – 40%[b)]	[24]
Resistant maltodextrins	Enzymatic starch hydrolysis with α(1→4) glucan hydrolases	α(1→4), α(1→4,6)	4 - 10	15%	[24]
Resistant starch	Extraction and / or conversion of starch	α(1→4), α(1→4,6)	polymer	depending on starch source	[29]
XOS	Enzymatic hydrolysis of xylan; xylan hydrolysis with subcritical water	β(1→4)	2-4	<10%	[60]

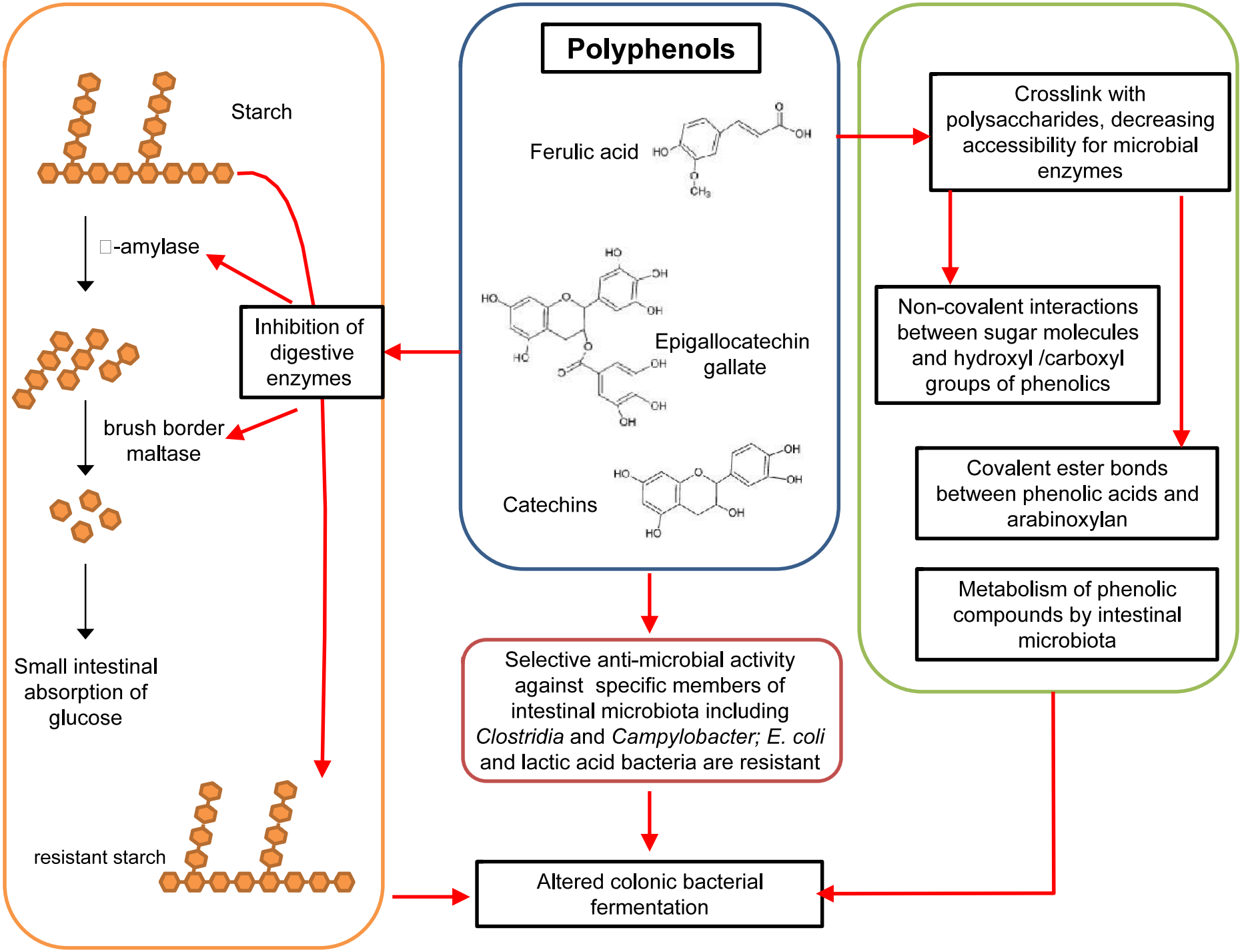
[a)]The digestibility of FOS and GOS is reduced in individuals with fructose malabsorption and in lactase non-persistent individuals, respectively. Lactosucrose digestion is initiated by brush border lactase; lactosucrose is thus indigestible in lactase-non-persistent individuals.

[b).]The digestibility of specific products depends on the removal of mono- and disaccharides by yeast fermentation, on the production method, and on the degree of polymerization.

Table 2. Beneficial and adverse health effects of prebiotic carbohydrates

General health benefits of carbohydrates with low small intestinal digestibility		
	Low cariogenicity	
	Reduced caloric content (60 – 75% of glucose)	[38]
Health benefits related to microbial production of short chain fatty acids		
	Intestinal motility	[61]
	Energy supply and proliferation of colonic mucosal cells	[41, 42, 62]
	Satiety, glucose homeostasis and insulin sensitivity	[63, 64, 65]
	Immune-modulation and improved epithelial barrier function	[66, 67]
	Reduced luminal pH, reduced colonic ammonia production, and pathogen exclusion	[68, 70]
	Improved iron absorption	[71]
Adverse health effects of FODMAPS and prebiotic carbohydrates		
	Induction of osmotic diarrhea by oligosaccharides when oligosaccharide load exceeds ~ 0.3 g / kg bodyweight	[36, 72]
	Excessive gas formation and intestinal bloating after rapid intestinal fermentation of carbohydrates	[36, 72]
Specific health benefits of dietary glycans that are unrelated to microbial metabolism and the prebiotic concept		
	Prevention of pathogen adhesion to intestinal cells	[21]
	Direct interaction with immune system	[73]
	Change of viscosity of intestinal content, increased secretion of bile salts and reduced cholesterol levels	[74, 75]


Major members of intestinal microbiota
Lactic acid bacteria, *Enterobacteriaceae*, bifidobacteria, *Bacteriodetes*
Bifidobacteria, *Bacteriodetes* *Roseburia* spp. *Faecalibacterium* spp. *Eubacterium* spp. *Coprococcus* spp.
Bifidobacteria, *Bacteriodetes* *Roseburia* spp. *Faecalibacterium* spp. *Eubacterium* spp. *Coprococcus* spp.
Dietary glycans
Plant cell wall polysaccharides
Acetate, propionate, butyrate, H_2, CO_2, CH_4
Polysaccharides
Acetate, propionate, butyrate, lactate, H_2, CO_2
Flatus, bacterial biomass, SCFA
Di-, trisaccharides
Lactate, acetate, succinate, 1,2 propanediol, H_2, CO_2
hydrolysis by brush border enzymes
terminal ileum
proximal colon
distal colon


Starch
-amylase
brush border maltase
Small intestinal absorption of glucose
resistant starch
Inhibition of digestive enzymes
Polyphenols
Ferulic acid
Epigallocatechin gallate
Catechins
Crosslink with polysaccharides, decreasing accessibility for microbial enzymes
Non-covalent interactions between sugar molecules and hydroxyl /carboxyl groups of phenolics
Covalent ester bonds between phenolic acids and arabinoxylan
Metabolism of phenolic compounds by intestinal microbiota
Selective anti-microbial activity against specific members of intestinal microbiota including Clostridia and Campylobacter; E. coli and lactic acid bacteria are resistant
Altered colonic bacterial fermentation