A Critical Look at Prebiotics Within the Dietary Fiber Concept

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Abstract

This article reviews the current knowledge of the health effects of dietary fiber and prebiotics and establishes the position of prebiotics within the broader context of dietary fiber. Although the positive health effects of specific fibers on defecation, reduction of postprandial glycemic response, and maintenance of normal blood cholesterol levels are generally accepted, other presumed health benefits of dietary fibers are still debated. There is evidence that specific dietary fibers improve the integrity of the epithelial layer of the intestines, increase the resistance against pathogenic colonization, reduce the risk of developing colorectal cancer, increase mineral absorption, and have a positive impact on the immune system, but these effects are neither generally acknowledged nor completely understood. Many of the latter effects are thought to be particularly elicited by prebiotics. Although the prebiotic concept evolved significantly during the past two decades, the line between prebiotics and nonprebiotic dietary fiber remains vague. Nevertheless, scientific evidence demonstrating the health-promoting potential of prebiotics continues to accumulate and suggests that prebiotic fibers have their rightful place in a healthy diet.

INTRODUCTION

A sufficiently high intake of dietary fiber (DF) is generally accepted as an essential component of a healthy diet. Although the positive influence of DF results directly from its low calorie content and its effects in the stomach and small intestine, a significant part of the beneficial health effects of DF is believed to arise from its fermentation in the colon.

The colon is heavily colonized by a diverse community of microorganisms, mainly bacteria. The gut microbiota is estimated to contain 10 times more cells than the human body and approximately 150 times more genes than the human genome (Ley et al. 2006, Qin et al. 2010). At present, it is widely accepted that the microbial inhabitants within the large bowel form a complex ecosystem that interacts with multiple host metabolic pathways (Tremaroli & Bäckhed 2012) and the host immune system (Karczewski et al. 2014, Tilg & Moschen 2015). Yet interest in the role of colonic microbiota in human health is relatively recent. It was only in the 1970s that growing concerns about antibiotic resistance and food safety drew attention to the microbial and metabolic activity in the large intestine (Brumfitt et al. 1971, Jones 1971). It was in these years that the first assumptions arose about a potential link between cancer and the intestinal microbiota composition (Moore & Holdeman 1975). Simultaneously, researchers gathered epidemiological data correlating the human diet and the prevalence of certain disorders (Burkitt et al. 1972, Trowell 1972).

Further knowledge of the microbial community, along with increasing evidence for the large bowel's role in numerous physiological processes within the host, inspired the development of concepts to steer and control the colonic ecosystem (Fuller 1989, Gibson & Roberfroid 1995). In this context, the term probiotic bacteria was introduced for a particular group of bacteria whose presence in a well-balanced intestinal microbial community is deemed advantageous; certain strains of bifidobacteria and lactobacilli were considered such (Fuller 1989). Furthermore, it has been suggested that intestinal bacteria can be classified according to presumed positive or negative impacts on host health; these classifications may also be linked to bacterial metabolic activity and, in particular, to their preference to derive energy from carbohydrate or protein substrates (Macfarlane et al. 2006, Manning & Gibson 2004). High prevalence of proteolytic bacteria (e.g., species of *Clostridium*, *Peptococcus*, *Peptostreptococcus*, and *Fusobacteria*) was considered detrimental because some typical metabolites of protein breakdown, including ammonia and phenolic compounds, may induce direct toxic effects (Visek 1978) or can act as (co)carcinogens (Bone et al. 1976). But the presumed negative effect of protein fermentation is mainly based on in vitro studies and, so far, cannot be demonstrated in humans (Windey et al. 2012a,b). Degradation of carbohydrates, however, yields mainly short-chain fatty acids (SCFAs) (acetate, propionate, and butyrate), which are not harmful at normal physiological concentrations and are acknowledged to have beneficial effects on the intestinal epithelium and gut immune system (Lee & Hase 2014).

On the basis of the growing body of evidence for a link between the human diet and the bacteria population in the large bowel (Cummings & Englyst 1987, Cummings & Macfarlane 1991), the term prebiotics was introduced for compounds that cause specific benign shifts in the colonic ecosystem. Prebiotics were considered positive for health, not only because of their good fermentability but also because they specifically stimulate beneficial colonic bacteria (Gibson & Roberfroid 1995). Recent advances in microbial community analysis confirmed the link between diet and gut bacterial composition (David et al. 2014, Salonen & de Vos 2014). Yet the latest studies also revealed the complexity of the gut microbiome and made the scientific community realize that establishing a causal link between bacterial shifts and host health is not straightforward.

In this article, concepts related to DF and prebiotics are further elaborated, and the thin line between prebiotic and nonprebiotic DF is discussed. An overview of the current knowledge of the health effects of DF is presented along with an articulation of the mechanisms that possibly

account for these effects. On the basis of this overview, the concept of prebiotics is placed in the context of DF, and suggestions for future research are articulated.

DIETARY FIBER

Definition

Numerous definitions of DF, with more or less subtle variations, have been proposed over the past decades (McCleary 2011). In 2008, the Codex Alimentarius Commission reached a consensus on this definition (Codex Aliment. Comm. 2009), describing DF as:

"Carbohydrate polymers with ten or more monomeric units, which are not hydrolyzed by the endogenous enzymes in the human small intestine and belong to the following categories:

- edible carbohydrate polymers naturally occurring in the food as consumed,
- carbohydrate polymers which have been obtained from raw materials by physical, enzymatic, or chemical means and which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities, and
- synthetic carbohydrate polymers which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities."

Two footnotes were added to the definition. One footnote states that the decision whether to include carbohydrates from three to nine monomeric units should be left to national authorities. The other footnote clarified the terms for inclusion of lignin and other noncarbohydrate plant compounds closely associated with DF polysaccharides. A last amendment on the latter footnote was published in 2010 (Codex Aliment. Comm. 2010).

The definition for DF published by the European Commission in 2008 is almost identical to that of the Codex Committee. However, nondigestible oligosaccharides with a degree of polymerization in the range of three to nine that belong to one of the three above categories are included as DF in the EU definition (Eur. Communities Comm. 2008). Also, other countries (e.g., Brazil, Canada, China, Australia, and New Zealand) decided to include these nondigestible oligosaccharides in the definition of DF in their national legislation (Jones 2014).

Classification

Apart from the classification inherent to the above-mentioned definition of DF, miscellaneous classification systems, mostly for naturally occurring DF, have been proposed. Naturally occurring DFs are sometimes classified according to their origin, mainly distinguishing DF derived from cereals, vegetables, and fruits (Cummings & Bingham 1987). An extensive classification of naturally occurring fiber is based on the chemical composition of those fibers, dividing DF into nonstarch polysaccharides, resistant oligosaccharides (including cellulose, hemicellulose, pectin, gums, mucilages, galacto-oligosaccharides, and fructans), resistant starch, lignin, and plant substances, such as waxes, phytate, cutin, saponins, suberin, and tannins, intricately tied to the nonstarch polysaccharide and lignin complex (AACC Diet. Fiber Defin. Comm. 2001).

Alternatively, fibers have been classified according to their physicochemical properties as either water soluble and mostly fermentable (such as pectin) or insoluble, less fermentable, and nonviscous (such as cellulose, lignin, and some of the hemicelluloses) (Anderson et al. 2009, Elleuch et al. 2011, Slavin et al. 2009). The soluble fibers can be further subdivided on the basis of their molecular size into two subcategories with differing rheological properties. Most polymeric soluble fibers are viscous (e.g., guar gum) and some are gel forming (e.g., pectin), whereas indigestible oligomers

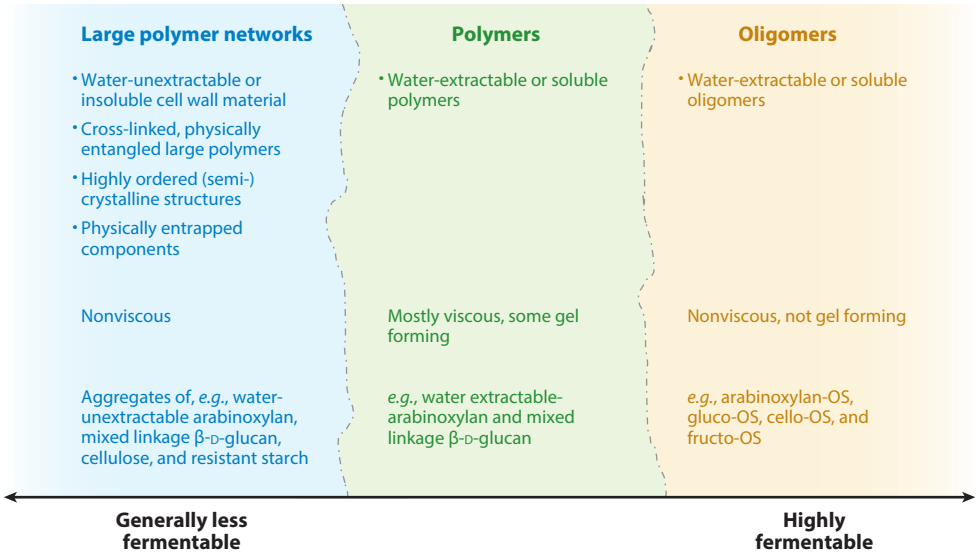

Figure 1

Three dietary fiber (DF) categories can be discerned on the basis of their physicochemical properties: oligomers, DF polymers, and DF-forming polymer networks. Oligomers are rapidly fermented by the colonic microbiota, whereas the DF forming polymer networks is usually fermented more slowly and in some instances to a limited extent; however, solubility and fermentability are not always correlated. Because these classes and their properties cannot be strictly delineated, the borders in the figure are represented by irregular lines. Abbreviation: OSs, oligosaccharides.

(such as oligofructose) are not viscous. The major exceptions are gum arabic, inulin, and arabinogalactan, which are soluble polymers that do not form highly viscous solutions (Tungland & Meyer 2002). **Figure 1** classifies DF on the basis of its physicochemical properties into three categories:

- DF oligomers
- DF polymers
- DF forming interpolymer networks.

In general, the extent and rate of colonic fermentation is believed to decrease from oligomers to polymers (Kelly 2009, Pollet et al. 2011, van de Wiele et al. 2007) and from water-soluble DF to water-insoluble DF (Guillon & Champ 2000). However, solubility and fermentability are not always strongly correlated (FAO 1998, Roland et al. 1995). Resistant starch, for instance, is insoluble and nonviscous but also highly fermentable. Thus, fermentability and solubility vary widely between different types of DF, and these properties allow placement of different DF types on a relative scale but do not allow for strict delineation of DF classes.

Furthermore, it is important to note that physicochemical properties of DF can change as a result of processing. In particular, solubilization of network-forming polysaccharides can be achieved by enzymatic degradation during food processing (Courtin & Delcour 2001, Damen et al. 2012b, Elleuch et al. 2011, Guillon & Champ 2000) and also occurs within the human colon by highly specialized gut bacteria (Flint et al. 2012a, Flint et al. 2012b).

Physicochemical Properties

The main physicochemical properties of fibers, which are associated with physiological effects in the gastrointestinal tract, are solubility, viscosity, particle size, adsorption, and water-holding

capacity. Solubility of isolated fibers evidently depends on their structure. Fibers with a highly stable crystalline structure in which the molecules are tightly arranged (e.g., cellulose) are typically insoluble. Conversely, isolated fibers with more irregularities in their configuration (e.g., side chains) tend to be soluble. Additionally, the presence of charged groups can affect solubility (Elleuch et al. 2011).

The viscosifying properties of DF in solution evidently depend not only on the structure of a particular DF but also on DF processing conditions (such as shear rate and temperature) (Dikeman & Fahey 2006). Specific DF-like pectins, gums, and mucilages form highly viscous solutions. Consequently, they can increase the viscosity of the luminal environment and affect transit and absorption of nutrients by intestinal cells (Theuwissen & Mensink 2008).

The adsorption capacity of a fiber relates to its potential to bind food substances such as water or minerals and endogenic substrates such as bile acids in the gastrointestinal tract. There is substantial evidence that the interactions of a particular soluble DF, such as β-glucan, with bile acids contribute to their cholesterol-lowering effect, although the exact mechanisms of interaction are not completely understood (Gunness & Gidley 2010, Mikkelsen et al. 2014). DF also generally interacts with water in a number of ways, including enclosure and hydrogen bonding (Chaplin 2003). The water-holding capacity of DF strongly depends not only on its chemical composition but also on physical characteristics such as particle size (Guillon & Champ 2000, Jacobs et al. 2015). In general, DF from algae has a higher water-holding capacity than that from fruit and cereals (Elleuch et al. 2011).

PREBIOTICS

The term prebiotic, first introduced by Gibson & Roberfroid (1995), was defined as "a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health" (Gibson & Roberfroid 1995, pp. 1405–6). A prebiotic index, representing the ratio of certain potentially beneficial bacteria, bifidobacteria and lactobacilli in particular, to malignant species, including clostridia, was proposed as a measure to quantify prebiotic potential (Palframan et al. 2003). Later, the definition was refined with three criteria. It stated that

- neither hydrolysis nor absorption in the stomach or small intestine may occur
- the ingredient is fermented by intestinal bacteria
- a selective response with regard to beneficial commensal bacteria in the colon is required (Gibson et al. 2004).

A growing number of studies have shown that the selective fermentation of indigestible compounds induces a wide variety of microbiological and metabolic changes in the ceco-colonic ecosystem, which may beneficially affect the host (De Preter et al. 2011). Gibson and the working group of the international scientific association of probiotics and prebiotics (ISAPP) described a dietary prebiotic as "a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health." (Gibson et al. 2010, p. 2). However, as discussed in the following section, the term selectively is rather ill defined in this definition because a clear distinction between beneficial and detrimental bacteria has not yet been set. Bindels et al. (2015) therefore recently proposed a fine-tuned definition of prebiotics: nondigestible compounds that, through their metabolism by microorganisms in the gut, modulate the composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect. So far, a wide variety of dietary carbohydrates, mainly oligosaccharides, have been presented as (candidate) prebiotics (Broekaert et al. 2011, Conway

Table 1 Functional carbohydrates presented as (candidate) prebiotics

Prebiotic	Structure	References
Fructo-OSs	α-D-Glu[-(1-2)-β-D-Fru]$_n$ ($n = 2$–4)	Conway 2001, De Vrese & Schrezenmeir 2008, Figueroa-González et al. 2011, Rastall & Maitin 2002, Roberfroid et al. 2010
Inulin	α-D-Glu[-(1-2)-β-D-Fru]$_n$ ($n = 10$–60)	Conway 2001, De Vrese & Schrezenmeir 2008, Figueroa-González et al. 2011, Rastall & Maitin 2002, Roberfroid et al. 2010
trans-Galacto-OSs	α-D-Glu-(1-4)-β-D-Gal[-(1-6)-β-D-Gal]$_n$ ($n = 1$–4)	Conway 2001, De Vrese & Schrezenmeir 2008, Figueroa-González et al. 2011, Rastall & Maitin 2002, Roberfroid et al. 2010
Soybean OSs	[α-D-Gal-(1-6)-]$_n$-α-D-Glu-(1-2)-β-D-Fru ($n = 1$–2)	Conway 2001, De Vrese & Schrezenmeir 2008, Figueroa-González et al. 2011, Rastall & Maitin 2002
Lactulose	β-D-Gal-(1-4)-β-D-Fru	Conway 2001, De Vrese & Schrezenmeir 2008, Rastall & Maitin 2002
Lactosucrose	β-D-Gal-(1-4)-α-D-Glu-(1-2)-β-D-Fru	De Vrese & Schrezenmeir 2008, Rastall & Maitin 2002
Xylo-OSs	β-Xyl[-(1-4)-β-D-Xyl]$_n$ ($n = 1$–8)	Cummings et al. 2001, De Vrese & Schrezenmeir 2008, Figueroa-González et al. 2011, Rastall & Maitin 2002
Arabinoxylan-OSs	Xylo-OSs with zero, one, or multiple L-arabinofuranose residues attached by α-1,2 or/and α-1,3 glycosidic linkages on the xylan backbone	Broekaert et al. 2011
Gentio-OSs	β-D-Glu[-(1-6)-β-D-Glu]$_n$ ($n = 1$–4)	De Vrese & Schrezenmeir 2008, Rastall & Maitin 2002
Resistant starch	α-D-Glu[-(1-4)-α-D-Glu]$_n$ ($n > 10$)	Fuentes-Zaragoza et al. 2011, Topping & Clifton 2001

Abbreviations: Fru, fructose; Gal, galactose; Glu, glucose; OS, oligosaccharide; Xyl, xylose.

2001, Cummings et al. 2001, de Vrese & Schrezenmeir 2008, Figueroa-González et al. 2011, Fuentes-Zaragoza et al. 2011, Rastall & Maitin 2002, Roberfroid et al. 2010) (**Table 1**).

WHAT DIFFERENTIATES PREBIOTIC FROM NONPREBIOTIC DIETARY FIBERS?

There is no clear-cut distinction between prebiotic and nonprebiotic DF. According to the first two criteria of Gibson et al. (2004), prebiotics need to be indigestible compounds that can be fermented by the colonic microbiota. However, in vitro fermentation trials (Jonathan et al. 2012) and clinical breath hydrogen tests (Oku & Nakamura 2014) indicate that fermentability is a rather continuous variable and cannot be the basis for a discrete classification of DF. Even cellulose, sometimes regarded as a nonfermentable substrate, is fermented to some extent in the human colon (Oku & Nakamura 2014, Stephen et al. 1987). The variability among individuals in gut community composition (Lahti et al. 2014) and colonic transit time (Burkitt et al. 1972) entails an interindividual variation in the degree of DF fermentation (Chassard et al. 2010, Chinda et al. 2004, Stephen et al. 1987) and further complicates a strict discrimination between fermentable and nonfermentable DF.

The third and last criterion for the conventional identification of prebiotics is the selective stimulation of beneficial intestinal bacteria. Traditionally, a selective increase in bifidobacteria or lactobacilli numbers has been assumed to be advantageous and sufficient to label a compound as prebiotic. However, the development of next-generation sequencing techniques has increased our

knowledge of the gut microbiome and its complexity. Apart from bifidobacteria and lactobacilli, multiple other bacterial groups, such as butyrate-producing bacteria (Furusawa et al. 2013, Louis et al. 2014) or *Akkermansia muciniphila* (Dao et al. 2015, Everard et al. 2013, Shin et al. 2014), are likely to be required for a healthy status. Indeed, it appears that a highly diverse microbiome composition is associated with health (Cotillard et al. 2013, Le Chatelier et al. 2013). Studies attempting to identify the healthy microbiota core (de Vos & de Vos 2012, Salonen et al. 2012) demonstrated that the outcome of this assessment highly depends on analytical parameters such as analytical depth and threshold for detecting less abundant bacteria.

Bindels et al. (2015) argued that current knowledge is insufficient to distinguish beneficial from malignant bacteria and proposed to omit the selectivity criterion in the definition of prebiotics. Indeed, there is currently no well-defined general consensus about the optimal composition of the intestinal bacterial community. It is furthermore plausible that this optimal composition differs among individuals. Although this is debated (Jeffery et al. 2012), there seem to be a limited number of microbial community compositions across individuals, reflected by the occurrence of only three bacterial clusters or enterotypes (Arumugam et al. 2011). Each of these bacterial clusters may strive to obtain its own optimal balance rather than evolving to a single, uniform optimal bacterial composition. In this context, Lahti et al. (2014) applied concepts from ecology to understand variations in colonic microbial communities. They observed that several bacterial groups exhibit bimodal abundance distributions among individuals, and their abundances are associated with host factors that include age and health. These bistable groups, termed tipping elements, are potential new targets for steering the gut microbiota, but a causal relationship with health is still missing (Lahti et al. 2014).

In conclusion, lack of a consensus on the composition of a healthy gut microbiome hinders the correlation of bacterial shifts with health and complicates a tight delineation between prebiotic and nonprebiotic DF. The health effects of DF and prebiotics are therefore discussed together below.

HEALTH EFFECTS OF DIETARY FIBER AND PREBIOTICS

The health effects of DF are closely related to their physicochemical properties and, even more closely, to their solubility (Guillon & Champ 2000). In addition, the applied dose, the composition of the diet, the microbial composition, and the hormonal status are generally assumed to affect the physiological activity of DF.

The physiological effects attributed to DF consumption can be classified into two categories: local effects (e.g., reduced transit times, lower nutrient absorption), which occur in the gastrointestinal tract, and systemic effects (e.g., effects on glucose and lipid metabolism), which are observed outside the large intestine. However, several of the so-called systemic effects may evolve from local effects.

Effects of Dietary Fiber and Prebiotics on Stool Parameters

Although the utility of consumption of DF as treatment for chronic constipation seems limited (Muller-Lissner et al. 2005), some DF types increase fecal bulk and/or decrease intestinal transit time in healthy individuals (Cummings 1997). The bulking effect of DF varies widely among different DF types, and strong effects are seen with, for example, wheat bran (Cummings 1997, Müller-Lissner 1988). It is important to note, though, that although stool weight increases with increased fiber consumption, a plateau effect eventually occurs for intestinal transit time (Burkitt et al. 1972, Müller-Lissner 1988).

In general, nonfermentable DF brings about a stronger fecal bulking effect than fermentable DF. The former induces bulking owing to its physical presence (Cummings 1997). In addition, the high water-holding capacity of (especially) water-insoluble DF that persists in the colon has been suggested to increase bowel mass and to induce a plasticizing effect that reduces stool consistency (Graham et al. 1982). Yet the effect of DF on stool water content is relatively small, and its importance has been questioned (Tungland & Meyer 2002, Wyman et al. 1976).

Although it has been suggested that highly fermentable DF contributes to fecal bulk by promoting microbial growth (Tungland & Meyer 2002), many studies have indicated that it causes little or no fecal bulking (Cloetens et al. 2010, François et al. 2014, van Dokkum et al. 1999). Stool parameters may also be influenced by the production of SCFAs. Indeed, organic acids can control gastrointestinal motility (Cherbut 2003), possibly by stimulating colonic production of serotonin, a neurotransmitter and hormone that modulates gastrointestinal motility (Reigstad et al. 2015).

Prebiotics have been suggested to play a role in the prevention of specific types of diarrhea. Their potential positive effects are ascribed to selective stimulation of the growth of bacteria such as certain *Lactobacillus* species that then may aid digestion of lactose in lactose-intolerant individuals or that may help combat infections that potentially cause diarrhea (Gibson et al. 2004). Although some clinical studies report a positive outcome in preventing travelers' diarrhea (Drakoularakou et al. 2009) and reducing the relapse of *Clostridium difficile*–associated diarrhea (Lewis et al. 2005a), others reported no significant effects on the incidence of travelers' diarrhea (Cummings et al. 2001) or on antibiotic-associated diarrhea in elderly patients (Lewis et al. 2005b), or children (Brunser et al. 2006). These inconsistent results might be related to the multiple factors that play a role in the etiology of diarrhea, including pathogens that do not target the large intestine (Cummings et al. 2001).

Effects of Dietary Fiber and Prebiotics on Colonic Health

Colonic health is a complex physiological state influenced by a variety of interactions between host, intestinal bacteria, and external factors that affect the large intestinal physiology and metabolism. Some potentially beneficial effects of DF and prebiotics on bowel health are higher resistance against pathogenic colonization and reductions in the levels of toxins and/or carcinogens in the gut. Also, maintaining mucosal integrity and permeability in general are considered to contribute to colonic health.

Resistance against pathogenic colonization. Several animal studies demonstrated that intake of DF (Akhtar et al. 2012, Yun et al. 2003) and particularly oligomeric DF/prebiotics (Buddington et al. 2002, Eeckhaut et al. 2008, Guarner 2007) can prevent pathogenic infection in the gut or systemic infections, although results are not always consistent (Ten Bruggencate et al. 2003, 2004), possibly owing to the adverse effects of the low calcium diets used in the latter two studies (Ten Bruggencate et al. 2003, 2004). The primary mechanisms thought to prevent gut colonization and improve gut barrier function are discussed below.

Because acetate, propionate, and butyrate are acids with pKa values of approximately 4.8, the production of SCFAs upon carbohydrate fermentation decreases the intestinal pH (Cummings et al. 1987, Topping & Clifton 2001, Wong et al. 2006). The latter is relevant for gut health because colon pH, typically ranging from 5.6 in the proximal colon to nearly 7.0 in the distal colon (Cummings et al. 1987, Evans et al. 1988), affects the gut bacterial composition. Indeed, in vitro studies have suggested that reducing the colonic pH from 6.7 or 6.5 to 5.5 changes the microbial composition drastically (Duncan et al. 2009, Walker et al. 2005). Therefore, acidification of the colonic lumen as a result of saccharolytic fermentation is considered effective in lowering

the levels of pH-sensitive pathogens in the gut (Topping & Clifton 2001). Accordingly, Zimmer and coworkers (2012) observed a correlation between fecal pH and an abundance of pH-sensitive Enterobacteriaceae. Vegans and vegetarians, who typically consume more DF, had lower stool pH levels and Enterobacteriaceae numbers than omnivorous subjects (Zimmer et al. 2012).

As defined, prebiotics stimulate the growth of beneficial bacteria and therefore have the potential to prevent pathogen colonization by raising competitive pressure. Bacteria, and probiotics in particular, can increase resistance to pathogenic colonization by competing for nutrients or for adhesion to intestinal epithelial cells (Derrien & van Hylckama Vlieg 2015) and by producing compounds with antibiotic or immunomodulating effects (Bron et al. 2012, Donia & Fischbach 2015). It has also been suggested that specific prebiotic oligosaccharides can prevent binding of pathogens at the mucosal surface by acting as receptor sites in the gut lumen (Gibson et al. 2005) and that specific oligomers, such as chito-oligosaccharides, exert antimicrobial activity (Hirano & Nagao 1989). However, so far, efficient inhibition of growth of pathogens by one of these specific mechanisms has been observed almost exclusively in vitro and in animals. This makes it difficult to deduce the importance of each individual effect for humans. Furthermore, DF and prebiotics can affect the host immune system and the gut barrier function, which also contributes to pathogen resistance. This is explained below.

Integrity of the mucus layer and the colonic epithelium. A successful prevention of infections requires appropriate actions of the host's defense system. The mucosal barrier is one of the body's primary defense mechanisms. It acts not only as a barrier that protects the underlying intestinal epithelium against chemical and biological hazards, but it also delivers immunoregulatory signals (Shan et al. 2013). The intake of fermentable DF is expected to positively impact the integrity of the mucosal and epithelial layers owing to the formation of SCFAs, which have a beneficial impact on the gut barrier (Tan et al. 2014). Indeed, SCFAs have been associated with higher colonic blood flow, epithelial cell proliferation, and cell differentiation (Kvietys & Granger 1981, Mortensen et al. 1991, Sakata 1987), as well as increased *MUC2* gene expression (Burger-van Paassen et al. 2009) and anti-inflammatory and antiapoptotic effects (Fukuda et al. 2011, Maslowski et al. 2009, Tilg & Moschen 2015). Butyrate has particularly positive effects, as it is the preferred substrate for the epithelial cells. Moreover, it improves the gut barrier by inducing a depletion of local O_2 levels in the gut epithelium, thereby stabilizing a hypoxia-inducible factor that modulates barrier protection (Kelly et al. 2015). Furthermore, SCFAs may stimulate production of gut peptides such as glucagon-like peptide 2 by endocrine L cells (Druart et al. 2014). The latter is involved in fructan-mediated improvement of gut barrier function in obese mice (Cani et al. 2009). The selective stimulation of beneficial bacteria such as *A. muciniphila* may be an additional mechanism by which prebiotics improve barrier function because this organism improves the integrity of gut epithelium in vitro (Reunanen et al. 2015). Poorly fermentable fibers are less likely to impact the mucus layer and colonic epithelium (Tungland & Meyer 2002), although they also influence colonocyte proliferation, possibly by their abrasive action (Folino et al. 1995). Finally, antioxidant activity of fructan was recently cited to explain its in vitro protective effect on the (sub)mucosal layers against protein oxidation (Pasqualetti et al. 2014).

Anticarcinogenic activity. Today, there is much interest in the potential anticarcinogenic properties of DF and prebiotics. Although the role of DF in colorectal cancer (CRC) development is still debated (Song et al. 2015), a meta-analysis of 25 prospective observational studies indicated that diets enriched in DF, and in cereal fiber and whole grains in particular, are associated with a reduced risk of CRC (Aune et al. 2011). On the basis of an extensive cohort study, Park et al. (2011) concluded that intake of DF from grains, but not from other sources, is significantly

inversely related to total cancer death. The inverse relationship between DF consumption and cancer mortality is in line with the outcome of the recent meta-analysis by Liu et al. (2015).

Several mechanisms have been put forward to explain the potential protective role of prebiotics and DF in the onset of CRC. First, DF reduces the transit time and dilutes luminal contents, which decreases the contact of the epithelial cells with potentially harmful products (Gear et al. 1981). Second, DF with adsorption capacity may bind and remove potentially harmful compounds in the colon (Gunness & Gidley 2010, Mikkelsen et al. 2014). Third, fermentable fibers and prebiotics in particular may have a positive impact by shifting the activity and/or composition of the microbial community.

Recent next-generation sequencing studies revealed changes in the microbiota composition upon CRC development, and several bacterial groups were proposed to play an active role in tumor initiation (Tjalsma et al. 2012, Zackular et al. 2014). The colonic microbial community can produce many potential carcinogens, such as secondary bile acids, but also protective metabolites (Irrazábal et al. 2014, Louis et al. 2014). The SCFAs produced upon DF fermentation, and butyrate in particular, possess anti-inflammatory effects (Maslowski et al. 2009, Singh et al. 2014), inhibit cancer cell proliferation (Bindels et al. 2012), and selectively induce apoptosis in CRC cells (Louis et al. 2014). However, results on the effects of butyrate administration in different CRC cell lines and in different animal models are not always consistent (Garrett 2015, Hamer et al. 2008), and conclusive evidence for anticarcinogenic properties of butyrate in vivo in humans is still lacking (Belcheva et al. 2015).

Apart from their direct effects, SCFAs also impact the intestinal environment by decreasing the pH. A reduced intestinal pH can repress protease activity and thus impair protein fermentation (Macfarlane et al. 1988). The absorption of ammonia, a potential carcinogenic product of protein fermentation, is hindered at low pH because ammonium ions are less diffusible than ammonia (Wong et al. 2006). DF fermentation and the resulting pH decrease also have the potential to affect bile acid metabolism. Rafter et al. (1986) concluded that, at a pH of 6 or below, bile acids are largely protonated and insoluble and so would not be taken up by colonocytes. Furthermore, acidification caused by DF fermentation in the large bowel may reduce the activity of bacterial enzymes, including 7α-dehydroxylase, which is involved in the formation of secondary bile acids (Christl et al. 1995, Rafter et al. 1986). Rat studies indicated the inhibition of dehydroxylation of primary bile acids upon carbohydrate fermentation (Andrieux et al. 1989). In humans, reduced fecal deoxycholic acid concentrations were related to an increase in fecal butyrate and propionate excretion (van Munster et al. 1994).

In addition to 7α-dehydroxylase, other bacterial enzymes (e.g., nitroreductases, azoreductases, β-glucosidases, and β-glucuronidases) that enable conversions of relatively harmless compounds to reactive toxic metabolites (Goldin 1990, Lim et al. 2005) show lower activity or are expressed to a lesser extent in more acidic environments (Ballongue et al. 1997). Nondigestible carbohydrates can also repress protein catabolism owing to their prolonged presence in the hindgut (Vince & Burridge 1980), which also stimulates microbial growth and in turn results in a higher net uptake of nitrogen-containing substrates by bacteria, including those that are potentially harmful (Geboes et al. 2006). In line with the above, the consumption of specific nondigestible carbohydrates decreases protein fermentation in animals and in humans (Cloetens et al. 2010, Damen et al. 2012a, Damen et al. 2011), which coincides in some cases with a reduction of the cytotoxicity of fecal water (Windey et al. 2014). Yet this does not necessarily imply a causal relationship between protein fermentation and fecal water cytotoxicity.

Furthermore, the link between protein fermentation and an increased risk of CRC development in humans has not yet been clearly demonstrated, possibly owing to the stronger effect of other dietary compounds or the influence of the protein source (Louis et al. 2014). Conversely, a low

DF intake combined with a high fat intake has a negative impact on mucosal biomarkers of cancer risk in humans (O'Keefe et al. 2015) and is likely to increase CRC risk.

Taken together, multiple mechanisms have been described to explain the protective potential of DF. The relevance of each individual mechanism is not completely understood, however, because most studies have focused on early markers rather than on examining hard end points related to colon carcinogenesis in humans. Nevertheless, DF and a healthy diet in general are presumed to have protective effects. Indeed, in 2011, the Continuous Update Project expert panel of the World Cancer Research Fund International and the American Institute for Cancer Research concluded that the evidence for a protective effect from foods containing DF against CRC is convincing (World Cancer Res. Fund Am. Inst. Cancer Res. 2011).

Effects of Dietary Fiber and Prebiotics on Mineral Absorption in the Colon

The intestinal pH is considered the predominant factor affecting the absorption of minerals in the large bowel. Lower luminal pH values caused by DF fermentation improve mineral solubility and may counteract the formation of bivalent cation-phytate complexes (Dendougui & Schwedt 2004, Lopez et al. 2000). Alternatively, organic acids can stimulate the proliferation of mucosal cells, resulting in a larger absorptive surface on the colonic mucosa. Furthermore, mineral absorption improves in rats upon fermentation of fructo-oligosaccharides because of the increased production of mucosal calcium-binding proteins (Fukushima et al. 2005). In addition, an increased blood flow, which is associated with colonic fermentation and the formation of SCFA, could promote cation absorption (Delzenne 2003).

Accordingly, consumption of nondigestible carbohydrates, oligosaccharides in particular, has been reported to stimulate the absorption of calcium and/or magnesium in rodents (Demigne et al. 2008, Wang et al. 2010, Weaver et al. 2011) and healthy humans (Coudray et al. 1997, van den Heuvel et al. 1999), and to increase bone mineral density in young adolescents (Abrams et al. 2005). Yet the effects on mineral absorption in clinical trials (reviewed by Scholz-Ahrens et al. 2001, Kelly 2009), are not always consistent. Despite the interindividual response variability, current data suggest that consumption of specific nondigestible carbohydrates, particularly oligosaccharides, may have a positive impact on absorption of specific minerals in some population subsets, particularly adolescents and postmenopausal women (Kelly 2009, Scholz-Ahrens et al. 2001). The impact depends, however, on the fiber type. Calcium absorption is negatively correlated with total DF consumption in postmenopausal women (Ramsubeik et al. 2014). This is possibly the result of the mineral binding capacity of, for example, wheat bran, which is rich in DF and binds calcium in vitro (Weaver et al. 1996).

Effects of Dietary Fiber and Prebiotics on Metabolic Syndrome

Metabolic syndrome is usually described as a cluster of metabolic abnormalities that include abdominal obesity, impaired glucose and lipid homeostasis, and elevated blood pressure, and it entails a higher risk of developing type 2 diabetes mellitus and cardiovascular disease (Grundy et al. 2005). Controlled clinical trials indicate that increased DF intake has a beneficial role in weight management; it may reduce blood pressure, particularly in hypertensive individuals, and viscous fibers have hypocholesterolemic effects and improve glycemia and insulin sensitivity (Anderson et al. 2009). In addition, epidemiological studies support the hypothesis that a diet rich in DF is associated with a decreased risk of cardiovascular disease (Threapleton et al. 2013).

Multiple mechanisms may be responsible for a positive effect of DF on insulin secretion and glucose and lipid metabolism. First, DF can reduce and/or slow down the release of nutrients

(e.g., glucose) in the blood stream in different ways. Indeed, the absorption of dietary fat, protein, carbohydrates, water, and electrolytes can be lowered by DF, which decreases small intestinal transit time as observed for lactulose (Holgate & Read 1983). Specific, viscous fibers such as guar gum and pectin slow down gastric emptying by increasing the viscosity of the food mass (Blackburn et al. 1984, Flourie et al. 1984, French & Read 1994, Leeds et al. 1981). A higher viscosity in the intestinal lumen can also hamper the absorption of glucose by decreasing the intraluminal diffusion and increasing the thickness of the unstirred layer on the absorbing surface (Flourie et al. 1984, Mälkki & Virtanen 2001).

Second, intake of specific viscous DF can increase the excretion of endogenous substrates such as bile acids, which are involved in lipid metabolism. This effect can be attributed mainly to the interaction of viscous fibers such as β-D-glucan with bile salt micelles (Mikkelsen et al. 2014), which thereby reduces the (re)absorption of cholesterol and bile acids (Daou & Zhang 2012, Theuwissen & Mensink 2008).

Third, SCFAs can directly affect glucose and lipid metabolism. Propionate, in particular, is a precursor in gluconeogenesis. Colonic acetate can contribute to cholesterol synthesis (den Besten et al. 2013). In contrast, propionate is believed to counteract such synthesis (Vipperla & O'Keefe 2012, Wolever et al. 1991). Yet SCFAs, in their role as signaling molecules, may have a bigger impact on glucose and lipid metabolism. Indeed, SCFAs can positively affect metabolism by mediating intestinal production of satiety-inducing hormones, including glucagon-like peptide 1 (GLP-1) (Tolhurst et al. 2012), and may promote the adipocyte production of leptin, which improves insulin sensitivity and controls satiety (Zaibi et al. 2010). Colonic acetate can cross the blood-brain barrier in rats and produce appetite suppression at the level of the hypothalamus (Frost et al. 2014). Furthermore, recent evidence suggests that butyrate activates intestinal gluconeogenesis (IGN) by changing gene expression in enterocytes, whereas propionate stimulates it via a gut-brain neural circuit. IGN stimulation causes beneficial effects on food intake and glucose metabolism in rodents (De Vadder et al. 2014). Animal studies also suggest that the positive metabolic effects of SCFAs are the result of increased energy expenditure (Gao et al. 2009, Kimura et al. 2011). In addition, multiple animal studies have shown that intake of prebiotics, which are easily converted to SCFAs, can have positive effects on glucose metabolism, lipid metabolism, and food intake (Roberfroid et al. 2010). Yet prebiotics affect not only SCFA production but also the microbiota composition, which possibly also ameliorates certain aspects of metabolic diseases. Indeed, animal studies (Ridaura et al. 2013, Turnbaugh et al. 2006) and one clinical trial (Vrieze et al. 2012) suggest that the gut microbiota plays a causal role in metabolic disorders. Small intestinal infusion of the fecal microbiota from lean donors improved peripheral insulin sensitivity in obese men (Vrieze et al. 2012). Nevertheless, results on the impact of prebiotics in humans on metabolic health are less conclusive. Kellow et al. (2014) reviewed the available data from randomized controlled clinical trials and concluded that the effects of prebiotic supplementation on body weight, energy intake, peptide YY and GLP-1 concentrations, insulin sensitivity, lipid levels, and inflammatory markers are equivocal. However, current evidence supports a positive effect of prebiotic intake on satiety and on postprandial glucose and insulin concentrations (Kellow et al. 2014).

It can be concluded that the metabolic effects of SCFAs in humans are not yet completely understood (Layden et al. 2013) and warrant further investigation. Short-term intervention trials corroborate that prebiotics improve satiety and postprandial glucose and insulin concentrations, but long-term trials are now required to confirm these effects. Results on other metabolic effects induced by prebiotics are inconclusive. Conversely, the positive effects of some DFs that increase the viscosity of the meal bolus are well established. Indeed, several authorities consider that a cause-and-effect relationship has been established between the intake of specific water-soluble fiber such as oat β-D-glucan and a reduction of postprandial glycemic response (EFSA Panel Diet.

Prod. Nutr. Allerg. 2010, 2011a,b), maintenance of normal blood cholesterol levels (EFSA Panel Diet. Prod. Nutr. Allerg. 2010, 2011a), and a potentially lower risk of developing coronary heart disease (US Dep. Health Hum. Serv. Food Drug Adm. 2006).

Effects of Dietary Fiber and Prebiotics on the Immune System

The gut-associated lymphoid tissue is the largest component of the body's immune system and fulfills a central role in the defensive functions in the large bowel. The immune system is constantly triggered by specific bacterial antigenic structures such as lipopolysaccharides, peptidoglycan, polysaccharide A, lipoteichoic acids, lipoproteins, and microbial nucleic acids (Lugo-Villarino & Neyrolles 2015). These structures are identified by pattern-recognition receptors and provoke several responses that are critical for maintaining intestinal barrier integrity and host microbial homeostasis (Hooper et al. 2012, Karczewski et al. 2014). Today, it is clear that probiotic bacteria can improve gut barrier function (Ohland & MacNaughton 2010) and can trigger immune responses such as defensin induction or secretory immunoglobulin A secretion (Derrien & van Hylckama Vlieg 2015). Some types of DF (Schley & Field 2002, Volman et al. 2008), particularly prebiotic DF (Kellow et al. 2014, Roberfroid et al. 2010), also induce immunomodulating effects, including elevations in the levels of fecal secretory immunoglobulin A and alterations in cytokine production and numbers of lymphocytes. The observed changes in immune responses upon consumption of prebiotics are often ascribed to beneficial alterations in the microbiota composition, given the well-documented immunological effects of probiotic bacteria. The production of SCFAs and increased mucus production were also postulated as potential underlying mechanisms (Schley & Field 2002). In this context, animal studies have demonstrated that SCFAs contribute to gut barrier function and are crucial for gut immunological homeostasis through multiple mechanisms (Furusawa et al. 2013, Lee & Hase 2014, Maslowski et al. 2009, Smith et al. 2013). Finally, recent in vitro studies suggest that DF also possesses direct immunomodulating effects because of its ability to directly bind Toll-like receptors (Bermudez-Brito et al. 2015; Vogt et al. 2013, 2014).

Clearly, there is promise in that the collective changes observed in immune responses point to a higher vigilance of the defense system after intake of DF and prebiotics. Unfortunately, the relevance of these results remains inconclusive owing to the absence of validated biomarkers on health or disease in humans (Albers et al. 2013, Calder et al. 2013, O'Flaherty et al. 2010).

Adverse Effects of Dietary Fiber and Prebiotics

Diarrhea, bloating, abdominal cramps, and flatulence are the dominant adverse symptoms associated with high intake of DF (Am. Diet. Assoc. 2008, Cummings & Macfarlane 2002). The occurrence of adverse effects upon fiber consumption is largely dose dependent. Although some studies have demonstrated that unwanted symptoms readily occur at approximately 10–20 g/day of DF and prebiotics (Kelly 2009), others reported that similar or even higher doses are well tolerated (Cloetens et al. 2010, de Vrese & Schrezenmeir 2008). Some fibers, because of their osmotic effect, induce diarrhea when consumed above a certain level (Clausen et al. 1998, Marteau & Flourié 2001). In addition, gaseous fermentation products such as hydrogen gas and carbon dioxide can cause flatulence at lower levels of intake (Kelly 2009). Large interindividual variations have been reported. Also, at moderate levels of intake, slowly fermented fiber types result in fewer side effects than their highly fermentable counterparts (Kelly 2009). Accordingly, a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (i.e., FODMAPS) has been shown to reduce symptoms in patients suffering from irritable bowel syndrome (Barrett 2013, Halmos et al. 2014).

Excessive DF consumption has the potential to have a negative impact on the absorption of nutrients such as certain vitamins and minerals. Nevertheless, this is unlikely to occur when healthy individuals consume DF within the range of recommended amounts (Am. Diet. Assoc. 2008).

CONCLUSIONS AND PERSPECPECTIVES

Although DF is an essential component of a healthy diet, the specific health effects of DF are debated, and only a minority of the proposed health claims has been approved (**Table 2**). Strong evidence exists for the association between the consumption of specific types of fiber and fecal bulking, decreased transit time, reduction of postprandial glycemic response, maintenance of normal blood cholesterol levels, and a lower risk of developing coronary heart disease. As a result, health claims on specific DFs for these effects have been approved by several official authorities such as the European Food Safety Authority (EFSA) (EFSA Panel Diet. Prod. Nutr. Allerg. 2010, 2011a,b) and the United States Food and Drug Administration (US FDA) (US Dep. Health Hum. Serv. Food Drug Adm. 2006). There is evidence that specific DFs improve resistance against pathogenic colonization, improve the integrity of the epithelial layer, reduce the risk of developing CRC, increase mineral absorption, and positively impact the immune system (**Table 2**). However, the underlying mechanisms are not clearly understood. The formation of SCFAs has often been invoked to explain these effects together with the positive impact on microbiota composition and activity. As argued above, such prebiotic effects cannot, by themselves, be seen as beneficial for health because of the limited knowledge on the composition and activity of a healthy microbiome. In order to establish a consensus on all health effects of the complete spectrum of DF, including prebiotics, at least three challenges need to be addressed in the future.

The first issue is that DF is a very general term that covers a heterogeneous group of compounds with varying (degrees of) physiological effects. This heterogeneity is often underestimated, which makes it difficult to understand the health effects of DF and the underlying mechanisms. Although desirable, many studies on the physiological effects of DF do not provide information on their molecular structure. A thorough analysis of the chemical structure is essential, though, especially when it comes to understanding the response of the microbial community in the colon. Accordingly, official authorities such as the EFSA and the US FDA demand a detailed characterization of food compounds before a health claim on DF can be assessed. The degree of polymerization, for instance, can vary widely among fibers within a chemical class; because polymerization impacts the physicochemical properties of fibers, and thus their physiological effects, it needs to be assessed.

A second concern is the need for more well-designed human intervention studies to establish a cause-and-effect relationship between thoroughly characterized DF and health. Although epidemiological or observational studies can show associations between specific DF types and their health-promoting potential, they do not provide a cause-and-effect relationship. In vitro and animal studies aid in understanding the underlying mechanisms and support results from clinical trials. Furthermore, changes in microbial numbers and immunological and other parameters need to be linked to health outcome measurements.

A third challenge is obtaining more insight into the interactions between DF, the microbiota, and host health. Modulation of the formation of SCFA and other bacterial metabolites is assumed to be involved in most positive effects of DF, but the implications for human health are far from being understood. The high interindividual variability of the human colonic microbiota needs to be taken into account and further complicates the exploration of this complex system. A multidisciplinary approach will be required to obtain a fundamental understanding of the DF-microbiota-host interactions and to link prebiotic-induced microbial shifts to human health.

Table 2 Overview of the current strength of evidence for the physiological effects of different DF types[a]

	Large polymer networks	Water-extractable polymers	Oligomers	References
Fecal bulking, increasing transit time	Generally accepted for specific DFs, effect generally less pronounced for soluble DF		ND	Cummings 1997
Resistance against pathogenic colonization	ND	ND	Positive outcomes mainly in animal studies	Guarner 2007
Integrity of epithelial layer	ND	Positive impact expected owing to SCFA formation	Positive impact expected owing to SCFA formation. Positive outcomes in animal studies	Cani et al. 2009, Kelly et al. 2015, Tan et al. 2014
Reduction of risk for developing colorectal cancer	Positive impact expected owing to, among other things, decreased transit time, binding toxic compounds, etc.	Positive impact expected owing to SCFA formation, mainly butyrate	Positive impact expected owing to SCFA formation, mainly butyrate	World Cancer Res. Fund Am. Inst. Cancer Res. 2011
Increase in mineral absorption in colon	ND	ND	Some positive effects are seen in specific population subsets, probably owing to SCFA formation	Kelly 2009, Scholz-Abrens et al. 2001
Reduction of postprandial glycemic response	ND	Generally accepted for specific DFs that increase viscosity	ND	Anderson et al. 2009; EFSA Panel Diet. Prod. Nutr. Allerg. 2010, 2011a,b
Maintenance of normal blood cholesterol levels	ND	Generally accepted for specific DFs that increase viscosity	ND	Anderson et al. 2009; EFSA Panel Diet. Prod. Nutr. Allerg. 2010, 2011b
Positive effects on the immune system	ND	Positive effects mainly in animals, possibly owing to SCFA formation	Positive effects mainly in animals, possibly owing to SCFA formation	Lee & Hase 2014, Roberfroid et al. 2010, Schley & Field 2002
Adverse effects	Largely dose- and individual-dependent	Largely dose- and individual-dependent	Largely dose- and individual-dependent, more likely to exert adverse effects	Am. Diet. Assoc. 2008, Kelly 2009

[a]Effects highlighted in dark green are generally accepted for specific DF types that belong to the indicated DF category. No strong evidence is available for the physiological effects highlighted in light green, though a positive impact is expected.
Abbreviations: DF, dietary fiber; ND, no (sufficient) data; SCFA, short-chain fatty acid.

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