

## Influence of Dietary Fibers on the Gut Microbiota

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### Abstract

The human gut is colonized by trillions of microorganisms, which form a complex microbial system. This super organ has important effects on human physiology, such as metabolizing food and xenobiotic compounds, contributing to the pathogenesis of metabolic diseases, and regulating colonic resistance against pathogenic bacteria. Dietary fibers have been proposed to modulate the gut microbiota. Considering the unique chemical and physiological properties of dietary fibers, these compounds may serve as important candidates for dietary intervention to elicit beneficial effects by altering the gut microbiota to a healthier state.

**Keywords:** Gut Microbiota; Dietary fiber; Health

### Gut Microbiota

The human gut harbors a vast array of microorganisms that form a complex microbial system. The commensal bacteria of the human microbiota typically include five microbial phyla: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria*. With *Firmicutes* and *Bacteroidetes* typically representing over 90% of the total gut microbiota for most individuals [1]. Most of the gut microbiota are non-culturable, but this notion has recently challenged by Goodman, *et al* [2] who reported that 99% of the bacteria that were characterized in the phylum, class, and order levels could be detected in a cultured fecal sample.

The colonization of the gut microbiota starts at birth, and the microbial composition changes through different stages of life. The infant acquires a gut microbiota from his or her mother and the environment. The most commonly isolated microorganisms from newborn feces are *Staphylococcus* spp., *Enterobacteriaceae*, and *Streptococcus* spp. [3], but the infant gut microbiota has a relatively simple structure and is unstable over time. Even different feeding strategies may affect the gut microbiota significantly. For instance, breast-fed infants have a less complex gut microbiota that is dominated by *Bacteroides* spp. and *Bifidobacteria* (over 90% of the total) compared with the formula-fed infants [3]. Ecological and evolutionary forces lead to a more stable microbiota in adults by shaping the microbial diversity. Later, a set of age-related shifts in the composition and function of the gut microbiota may occur, for instance, a significant decrease in *Bifidobacteria* and a declined in immune system responses, occur after the age of 60 years [4].

In addition to the mother's impact at birth, other factors have been suggested to influence the gut microbiota. First, the host genetic background may contribute to the individuality of the microbiota. Studies performed using mouse models indicated the linkage of quantitative trait loci (QTL) with specific microbiota composition, confirming the importance of genetic control in shaping the diversity of the microbiota [5]. Second, environmental factors, such as diet and exercise, have also been proposed as a driving force for the gut microbiota [6,7].

The gut microbiota has a huge metabolic capacity and can complement functions that have not developed within the human body [8], making the microbiota a "super organ" that is responsible for the digestion of complex food/drug components, metabolism and energy harvesting, colonization resistance and other functions [8,9].

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## The role of the gut microbiota in human physiology

### Gut microbiota and food/xenobiotic metabolism

The gut microbiota can either produce harmful metabolites associated with human diseases or beneficial components that protect against diseases, depending on dietary intake [10]. For instance, the toxic effect of melamine in infant milk is mediated by the biotransformation of these compounds by certain gut microbiota [11]. Moreover, the gut microbiota can metabolize dietary L-carnitine from red meat to trimethylamine-N-oxide, which is a proatherogenic compound [12], while the production of short chain fatty acids (SCFA) from carbohydrate fermentation, vitamins and conjugated linoleic acid may have beneficial health effects. Although we still have a limited understanding of the metabolism of different compounds by the gut microbiota, carbohydrate and polyphenol metabolism have been well studied.

Fruit, vegetables, and cereals are the major dietary components that provide dietary fibers for the microbiota. Thanks to at least 81 different glycoside hydrolase families, these fibers can be metabolized to sugars by the gut microbiota; these sugars are fermented to SCFA, including acetate, propionate, and butyrate. These SCFA can trigger the secretion of the hormone GLP-1, resulting in increased insulin secretion and decreased feeling of hunger [13]. Specifically, butyrate, which is a preferred energy source of gut epithelial cells, has been shown to promote energy expenditure and improve insulin sensitivity in a mouse model [14]. Saccharolytic fermentation is important because it may create a beneficial gut environment, in contrast, when carbohydrates are in short supply, the gut microbiota will switch to the fermentation of amino acids, resulting in the release of harmful metabolites including branched chain fatty acids (BCFA) and ammonia [15].

In addition to the complex carbohydrates, polyphenols are other non-digestible components in our daily diet than can be metabolized to a large extent by the gut microbiota, yielding products such as hydroxy phenylacetic, phenylpropionic, and phenylbutyric acids, which have potential health benefits [16]. For instance, The 3,4-dihydroxyphenylacetic and 4-hydroxyphenylacetic acid metabolites have been shown higher inhibition of platelet aggregation than their precursors (rutin or quercetin) [17]. The hydroxy phenylacetic and phenylpropionic derivatives from the microbial degradation of flavonoids have been linked to inhibit endothelial dysfunction [18].

### Gut microbiota and metabolic diseases

Metabolic syndrome (including insulin resistance, hyperglycemia, hypertension, and dyslipidemia) is a cluster of obesity-related disorders that affects 35% of adult Americans [19]. The increasing metabolic syndrome epidemic results from an energy imbalance that involves the consumption of more calories than expended and is characterized by increased risk of type-2 diabetes and other metabolic diseases. Recent studies have suggested the existence of a strong association between the gut microbiota and metabolic syndrome [20,21].

### Gut microbiota and obesity

The first study to link obesity with the gut microbiota profile was conducted in genetically obese mice and reported that obesity is associated with different microbiota at the phylum level, with an increased prevalence of *Firmicutes* and a decreased prevalence of *Bacteroidetes* in obese mice in comparison to their lean counterparts [22]. Consistent with the mouse data, the first human study also showed a higher proportion of *Bacteroidetes* in normal weight individuals than the obese individuals [23]. However, some subsequent studies have reported differing results. For instance, Collado, *et al.* reported significantly higher level of *Bacteroidetes* in overweight women than in normal-weight individuals [24]. The failure of the Human Microbiome Project to find an association between the *Firmicutes/Bacteroidetes* ratio and obesity also raise the questions about whether this ratio should be associated with obesity [25].

Compositional changes in the gut microbiota in response to weight loss have been reported, but the results are also inconsistent. For instance, Schwartz, *et al.* reported a decrease in *Bacteroidetes* after weight loss [26], while Duncan, *et al.* reported no change in *Bacteroidetes* after a 4-week carbohydrate-reduced diet [27]. These mixed results may be explained by the complexity of the gut microbiota and the existence of large individual differences.

Rather than compositional differences at the phylum level, species-level bacterial differences are more likely to be responsible for the association between diseases, such as obesity, and the gut microbiota, because the function of gut microbiota diverges at the species level [28]. For instance, the consumption of *Bifidobacterium longum* decreased the expression of genes that encode inflammatory cytokines, but the ingestion of *Bifidobacterium animalis sub sp. lactis* elicited a different effect, resulting in an increase in anti-inflammatory cytokines [29,30]. Moreover, *Akkermansia muciniphila*, which is a mucin-degrading bacterial species, has been inversely correlated with body weight in rodents and humans [31]. A previous study also demonstrated the specific function of *A. muciniphila*, including the reversal of high fat-induced weight gain, adipose inflammation, and insulin resistance [31].

Although recent studies have suggested the core microbiota composition is associated with different health or disease states, such as obesity, the problem of whether an altered gut microbiota causes the obese state or the obese state results in an altered gut microbiota is of interest. The applicability of the results to humans is in debate because the physiology and metabolic pathways of these animals are quite different from those of animals with conventional gut flora. An emerging view suggests that the gut microbiota is characterized by a core metabolic function rather than by certain types of bacteria; thus, even distantly related bacteria share similar key metabolic functions and these key metabolic functions are directly related to health or disease [32]. For instance, the gut microbiota may impact the genesis of obesity through metabolic products or between microbiota-host signaling.

Potential mechanisms that link the gut microbiota with obesity have been proposed. First, through the digestion of complex dietary carbohydrates, the gut microbiota can produce SCFA, including acetate, propionate, and butyrate. These organic acids not only represent an energy source, but also trigger cell-specific signaling cascades, regulating energy harvest. For instance, G-protein coupled receptors (GPCRs), GPR41 and GPR43 have been shown to be activated by SCFA, eliciting a cascade reaction. The activation of GPR 41 can enhance the secretion of peptide YY (PYY) from intestinal L cells, inhibiting gastric emptying and food intake, whereas the activation of GPR43 is reported to inhibit fat accumulation in the adipose tissue and trigger the secretion of GLP-1, which is a peptide that inhibits gastric emptying and food intake [33,34]. Second, the gut microbiota can regulate host metabolism by regulating bile acids. Bile acids reach the colon, where they can affect the composition of the gut microbiota and are also modified by the gut microbiota [35]. The primary function of bile acids is to emulsify dietary lipids and fat-soluble vitamins, but these acids can also act as signaling molecules for two different receptors in the host: cellular farnesoid X receptor (FXR), which controls the transcription of genes that affect glucose, and lipid metabolism, and TGR5, which increases GLP-1 secretion [20]. Another study suggested that the bile salt hydrolase activity (BSH) of gut microbiota plays an important role in energy homeostasis. Significant reductions in weight gain, serum cholesterol, and liver triglycerides were observed in mice with elevated BSH activity [35]. Third, by acting on the mucus thickness or tight junction proteins, the gut microbiota may regulate the gut permeability, resulting in the genesis of low-grade inflammation that is characteristic of obesity and many obesity-associated disorders [36]. Cani, *et al.* has suggested that lipopolysaccharide (LPS), which is a constituent of gram-negative gut bacteria, may act as a trigger for this inflammation, a condition known as metabolic endotoxemia [36]. The altered gut microbiota associated with increased epithelia permeability resulted in the easy translocation of LPS to the blood and increased plasma levels of LPS. The LPS may subsequently be transported by a mechanism involving lipoproteins and trigger the secretion of proinflammatory cytokines (e.g., TNF- $\alpha$ , IL-1, and IL-6) after binding to the CD14 and TLR4 receptors on innate immune cells [20]. The proposed mechanism by which LPS causes inflammation and obesity was established using a mouse model. For instance, LPS-treated mice developed symptoms, such as increased body, liver, and adipose tissue weight gain to a similar extent as high fat-fed mice [37].

### Gut microbiota and type-2 diabetes

The rapid increase in the prevalence of type-2 diabetes in the recent decades makes this disease a worldwide health concern. Approximately 20-25% of the world's population has the problem of metabolic syndrome, including obesity, insulin resistance, hyperglycemia, and hyperlipidemia. This population is also at high risk for type-2 diabetes [38]. The gut microbiota plays a vital role in these pre-diabetes metabolic syndromes, such as obesity and insulin resistance. Cani, *et al.* established the association between the gut microbiota, inflammation, and pre-diabetes metabolic syndromes and suggested the bacterial LPS/CD14 system may regulate insulin

sensitivity. CD14 has been identified as a pattern recognition receptor (PRR) that binds LPS. In a four-week high fat diet, wild-type mice had increased in LPS accompanied by alternations in gut microbiota composition and insulin resistance [37]. In contrast, when CD14 knockout mice were subjected to the same high-fat diet, the genetically modified mice gained less weight and exhibited increased insulin sensitivity and reduced systemic inflammation compared with the wild-type mice. In contrast, the reinfusion of bacterial LPS to the CD14 knockout mice abolished all of these metabolic improvements [37]. In another experiment, obese mice treated with an antibiotic that altered the gut microbiota and decreased endotoxemia exhibited improvements in insulin resistance, fasting glycemia, and inflammatory parameters compared with control ob/ob mice [39,40]. Another study linked increased bacterial translocation with the onset of insulin resistance. Bacterial translocation is used to describe the migration of viable bacteria from the gastrointestinal tract to extra intestinal sites. For instance, increased *E. coli* translocation into the blood contributed to the establishment of diabetic status, whereas a probiotic treatment that decreased translocation could reverse the diabetic status [41]. These results may be associated with gut permeability as discussed in the obesity section, because obesity is one of the most important risk factors for type-2 diabetes.

### Gut microbiota and colonization resistance

Colonic resistance against intestinal pathogens is conferred primarily by the commensal gut microbiota, resulting in the protection of the host intestine. This phenomenon can be explained from an ecological perspective. The establishment of a healthy gut microbiota allows commensal organisms to occupy specific ecological niches according to specific nutritional states or metabolic functions. Once stability is established, the resilience of the gut system may protect it from infection with pathogenic bacteria. The colonization of commensal bacteria contributes to the homeostasis of the gut ecosystem by regulating the immune system and stimulating the production of antimicrobial factors. This phenomenon is of interest because with increased antibiotic therapy, antibiotic-resistant bacteria in the gut may proliferate in the intestinal lumen, posing a serious health threat.

### Dietary fiber as a treatment to modulate the gut microbiota

Dietary fiber can be divided into two classes based on solubility in water: soluble dietary fiber and insoluble dietary fiber. Pectin, guar gum, soluble  $\beta$ -glucan, and polysaccharide gums are examples of soluble dietary fiber. Soluble dietary fiber shows favorable effects on controlling glucose level and lipid metabolism homeostasis, mainly due to an increased viscosity in luminal contents [42]. Hemicellulose, cellulose and lignin are among the common insoluble dietary fibers, which promote fecal bulking, softening and laxation. Both soluble and insoluble dietary fibers can be fermented by gut microbiota in the colon and yield SCFAs, although soluble generally results in comparatively more rapid and higher concentrations of SCFAs.

Different dietary fibers show quite different fermentation impacts on gut bacteria. For instance, *Bifidobacteria* and *Lactobacilli* cannot ferment cereal  $\beta$ -glucan alone *in vitro* but can utilize oligosaccharides resulting from its partial hydrolysis [43]. In contrast, *Bifidobacterium longum* and *Bifidobacterium adolescentis* can ferment long chain arabinoxylan (AX) *in vitro* from a variety of cereals without pre-hydrolysis. It is likely that different dietary fibers are more effective than others at modulating obesity since dietary fiber is a complex class of compounds.

### Fructans

Fructan is a general term for a wide variety of carbohydrates such as fructo-oligosaccharides (FOS), oligofructose, and inulin, depending on degree of polymerization (DP). Fructans reach the large colon and undergo fermentation by gut microbiota. FOS with low DP is mostly fermented in the proximal colon, while some inulin and fructans with longer DP may reach more distal regions of the colon [44]. The primary effect of inulin type prebiotics on gut ecology is the stimulation of bifidobacterial growth [45]. Inulin-type fructans may have an influence on weight loss, although research in this area is very limited. One dietary intervention study with 97 adolescents demonstrated a significant reduction in weight gain for the people receiving 8g/d oligofructose-enriched inulin compared with maltodextrin as a control for a year; the difference disappeared one year after the supplementation was stopped [46].

### Resistant starch

Some starch may escape digestion in the human small intestine and reach the colon to be fermented by gut bacteria. Resistant starch (RS) can be classified into 4 main types: physically inaccessible starch (RS-1), resistant granules and high amylose starches (RS-2), retrograded starches (RS-3) and chemically modified starches (RS-4; [47]). Fermentation of RS, especially by RS-2, has been shown to increase the production of butyrate. Another study showed that RS-4 but not RS-2 leads to profound phylum-level changes, significantly increasing *Actinobacteria* and *Bacteroidetes* while decreasing *Firmicutes* [48]. These studies indicate that differences exist in the fermentation properties of different type of RS, even though they are the same chemical structure. With regard to obesity, some studies show that inclusion of RS in the diet can reduce body fat by energy dilution and changing expression of PYY and GLP-1 [49].

### Arabinoxylan

AXs are the most abundant non-digestible carbohydrates present in most cereals. AX can be divided into water-extractable (WE-AX) and water-un extractable (WU-AX) according to extractability in water, as well as arabinoxylan oligosaccharides (AXOS), which are hydrolysis products of AX. AXs are broken down in the colon by intestinal bacteria that express AX-degrading enzymes such as xylanases and arabinofuranosidases [50]. Fermentation of AX by human intestinal bacteria *in vitro* is associated with a higher proportion of propionate production compared with other dietary fibers [51,52]. High fat mice supplemented with WE-AX, have shown increases in clostridial cluster XIV, *Bacteroides-Prevotella* spp., and *Bifidobacteria* accompanied by reduced circulating inflammatory markers, body weight, and hepatic cholesterol-lowering effects [53]. WE-AX cross-linked with ferulic acid resulted in a slower fermentation rate than non-cross-linked WE-AX, the latter of which has also been correlated to increases in *Bacteroides fragilis* *in vitro* [54]. WU-AX is only partially fermented in the colon, but stimulates butyrate and butyrate-producing bacteria such as *Roseburia/E. rectal* spp. [55].

### $\beta$ - Glucan

Mixed linkage (1,3 and 1,4)  $\beta$ -glucans are a ubiquitous group of non starch polysaccharides in cereal grains, but are found in the highest concentrations in oats and barley [56].  $\beta$ -glucan has been demonstrated in clinical trials to significantly impact weight loss by increasing satiety, influencing absorption efficiency in the small intestine and lowering cholesterol [57-59]. In addition,  $\beta$ -glucan has been documented to increase insulin sensitivity [60]. The health benefits of  $\beta$ -glucan in the gastrointestinal tract, such as increasing satiety and reducing blood serum cholesterol and blood glucose, are correlated with molecular weight distribution and viscosity. An increase in *Bifidobacteria* compared with none detected at baseline and significant increase of *Bacteroides* were observed by dietary intervention with  $\beta$ -glucan [61].

### Conclusion

Recent mechanistic studies in animal and human models have provided insight into the proposed contributory role of the gut microbiota in metabolizing food/xenobiotic compounds, contributing to the pathogenesis of metabolic diseases and regulating colonic resistance against pathogenic bacteria. Modulation of the gut microbiota composition or its biochemical capacity may be facilitated by dietary intervention. Considering the unique chemical and physiological properties of dietary fibers, dietary fibers may serve as important candidates for dietary intervention to elicit beneficial effects by altering the gut microbiota to a healthier state.

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