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Whole Food–Based Approaches to Modulating Gut Microbiota and Associated Diseases

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Abstract

Intake of whole foods, such as fruits and vegetables, may confer health benefits to the host. The beneficial effects of fruits and vegetables were mainly attributed to their richness in polyphenols and microbiota-accessible carbohydrates (MACs). Components in fruits and vegetables modulate composition and associated functions of the gut microbiota, whereas gut microbiota can transform components in fruits and vegetables to produce metabolites that are bioactive and important for health. The progression of multiple diseases, such as obesity and inflammatory bowel disease, is associated with diet and gut microbiota. Although the exact causality between these diseases and specific members of gut microbiota has not been well characterized, accumulating evidence supported the role of fruits and vegetables in modulating gut microbiota and decreasing the risks of microbiota-associated diseases. This review summarizes the latest findings on the effects of whole fruits and vegetables on gut microbiota and associated diseases.

INTRODUCTION

IBD: inflammatory bowel disease

MACs: microbiota-accessible carbohydrates

SCFAs: short-chain fatty acids

F:B: Firmicutes to Bacteroidetes

Trillions of microorganisms inhabit the large intestine. The main phyla are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia (Alonso & Guarner 2013). In recent years, studies about gut microbiota have flourished. An increasing number of diseases, such as obesity, inflammatory bowel disease (IBD), cardiovascular diseases, and metabolic syndrome, have been associated with dysbiosis of gut microbiota. The gut microbiota is influenced by many factors, including diet and health status (Zmora et al. 2019). Modulation of gut microbiota by diet is a promising and effective way to benefit the host. The effects of diet on the composition and function of gut microbiota can be beneficial or harmful. In general, dietary intake of whole fruits and vegetables has been known to beneficially affect gut microbiota by promoting the growth of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus* (Guglielmetti et al. 2013, Vendrame et al. 2011), and/or inhibiting the growth of harmful bacteria, such as *Escherichia coli* and *Enterococcus* spp. (Paturi et al. 2017) (**Figure 1**). Fruits and vegetables are rich in microbiota-accessible carbohydrates (MACs), such as oligosaccharides, pectin, cellulose, inulin, lignans, and resistant starches, which serve as substrates for certain beneficial bacteria (Brinkworth et al. 2009, Sonnenburg et al. 2016). The gut microbiota ferments MACs to produce short-chain fatty acids (SCFAs), which can in turn impact bacterial composition (Brinkworth et al. 2009, De Filippo et al. 2010, Zhou et al. 2017). Furthermore, polyphenols in fruits and vegetables can be degraded by gut bacteria to various metabolites, and both polyphenols and their metabolites can modulate gut microbiota. This review focuses on the effects of whole foods, e.g., fruits and vegetables, on gut microbiota and microbiota-associated disease, e.g., obesity and IBD.

INTERACTIONS BETWEEN WHOLE FOODS AND GUT MICROBIOTA IN DISEASE-FREE POPULATIONS

Whole fruits and vegetables are known to be good food choices to maintain and promote health. Various fruits and vegetables have been studied to determine their effects on gut microbiota in healthy, disease-free populations, including both humans and animals. This section provides a summary of the modulating effects of fruits and vegetables on the gut microbiota as well as the interactions between gut microbiota and the major bioactive components of fruits and vegetables. **Table 1** summarizes representative studies on the impacts of whole foods and their components on gut microbiota.

Whole Fruits and Vegetables Beneficially Impact Gut Microbiota

Among the major phyla of gut microbiota, Firmicutes and Bacteroidetes represent more than 90% (Alonso & Guarner 2013, Turnbaugh et al. 2006). Intake of whole fruits and vegetables may modulate the growth of Firmicutes and Bacteroidetes. A lowered ratio of abundance of Firmicutes to Bacteroidetes (F:B) is considered as a marker of healthier gut microbiota (Turnbaugh et al. 2006). Daily consumption of 200 g of cooked broccoli for 18 days in human volunteers reduced the relative fecal abundance of Firmicutes and increased that of Bacteroidetes. These effects were ascribed to fiber and glucosinolates found in broccoli (Kaczmarek et al. 2019). Human intake of cranberry (30 grams of freeze-dried powder per day for 5 days) also led to a decrease in the fecal abundance of Firmicutes and an increase in Bacteroidetes (Rodríguez-Morató et al. 2018). Consistent with these human studies, dietary treatment of mice with freeze-dried black raspberry powder (10% w/w in diet) for six weeks lowered the F:B ratio in the fecal microbiota (Gu et al. 2019). Feeding cooked navy bean or black bean to mice altered fecal microbiota composition with an increasing trend in the abundance of Bacteroidetes. The fecal abundance of *S24–7*, a

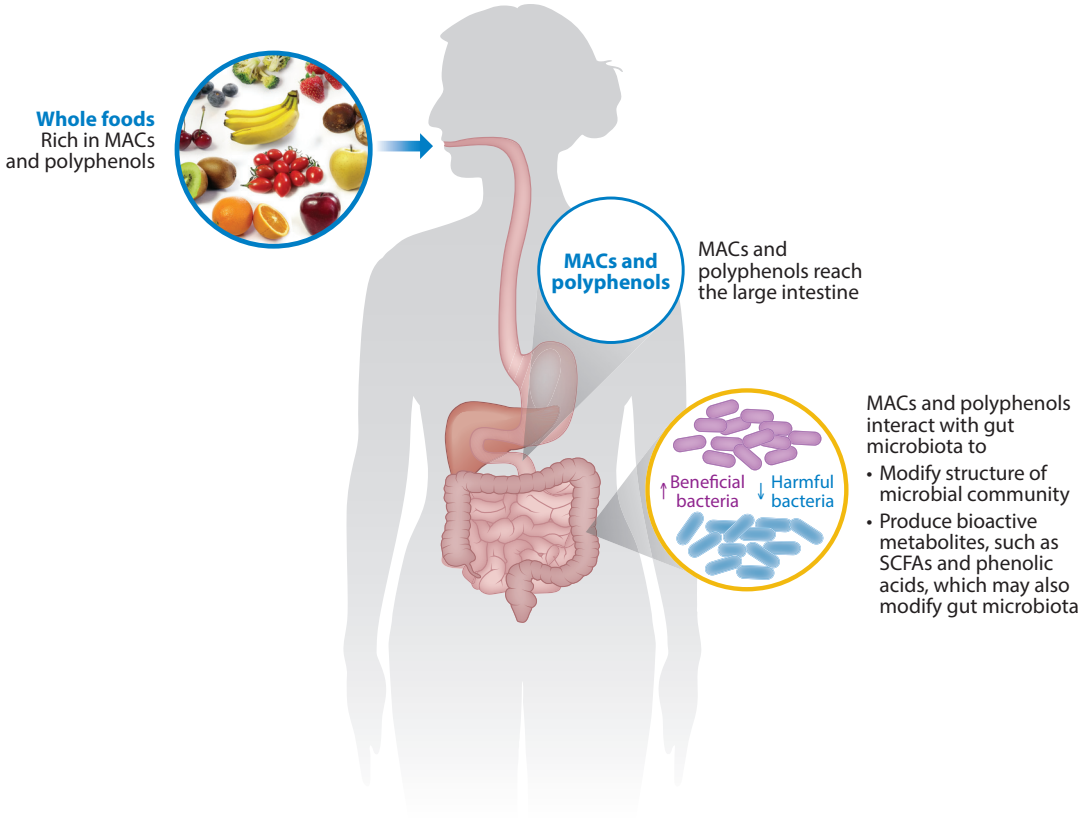

Figure 1

The interactions between whole foods and gut microbiota. Whole foods such as fruits and vegetables are rich in microbiota-accessible carbohydrates (MACs) and polyphenols. MACs, such as oligosaccharides, pectin, cellulose, inulin, lignans, and resistant starches, are resistant to digestion in the upper gastrointestinal tract prior to reaching the large intestine, where they interact with gut microbiota. This interaction may lead to altered gut microbiota and the production of short-chain fatty acids (SCFAs) from fermentation of MACs by microbiota, and SCFAs may also modulate microbiota composition. After consumption of whole fruits and vegetables, a large portion of their polyphenols accumulate in the large intestine, where they may interact with gut microbiota to modify the structure of the microbial community and produce bioactive metabolites, such as phenolic acids, via microbiota-mediated metabolism of polyphenols. The microbial metabolites of polyphenols may modulate gut microbiota as well. The overall outcome of interactions between whole foods and gut microbiota may be an increased abundance of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, and a decreased abundance of harmful bacteria, such as *Escherichia coli* and *Enterococcus* spp. Furthermore, SCFAs and phenolic acids may also interact with host tissues such as colonic epithelia to impact host health.

major family of Bacteroidetes, was significantly increased, and the fecal abundance of *Oscillospira*, *Ruminococcus gnavus*, *Lactococcus*, *Coprococcus*, and *Streptococcus*, all members of the Firmicutes, were remarkably decreased by the intake of the beans. Furthermore, concomitant with the altered fecal microbiota, dietary bean treatments enhanced multiple aspects of mucus and epithelial barrier integrity in the mouse colon (Monk et al. 2017).

Intake of whole fruits and vegetables can promote the growth of certain beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*. In human studies, oral intake of freeze-dried wild blueberry powder increased fecal abundance of *Bifidobacterium* and *Lactobacillus* (Guglielmetti et al. 2013, Vendrame et al. 2011). After simulated digestion, fermentation of whole apples (Renetta and Golden Delicious) with fecal bacteria from healthy donors promoted the growth of *Bifidobacterium*

Table 1 Effects of whole fruits and vegetables on gut microbiota in disease-free populations

Source	Whole foods or extracts	Model	Dose	Duration	Effects on gut microbiota	Reference
Apple	Fresh apple	Human	Oral, 2 apples/(person·day)	2 weeks	↑*Bifidobacterium*, ↑*Lactobacillus*, ↑*Streptococcus*, ↓*Enterobacteriaceae*, ↓*Pseudomonas*	Shinohara et al. 2010
	Raw whole apple	Rats	10 g/day in diet	4 weeks	↓*Bacteroides*	Licht et al. 2010
	Apple pectin	Rats	7% w/w in diet	4 weeks	↑*Anaeroplasma*, ↑*Anaerostipes*, ↑*Roseburia*, ↑*Clostridium coccoides*, ↓*Alistipes*, ↓*Parabacteroides* sp., ↓*Bacteroides*	
Black raspberry	Freeze-dried black raspberry powder	Mice	10% w/w in diet	6 weeks	↓*Clostridium*, ↓*Lactobacillus*, ↑*Barnesiella*,	Gu et al. 2019
	Freeze-dried black raspberry powder	Mice	10% w/w in diet	7 weeks	↓Firmicutes, ↑Bacteroidetes, ↑Verrucomicrobia, ↑*Akkermansia muciniphila*	Tu et al. 2018
	Freeze-dried black raspberry powder	Rats	5% w/w in diet	6 weeks	↑*Anaerostipes*, ↑*Akkermansia*, ↑*Desulfovibrio*, ↑*Ruminococcus*, ↑*Coprobacillus*, ↓*Acetivibrio*	Pan et al. 2017
	Anthocyanins from black raspberry	Rats	0.2% w/w in diet	6 weeks	↑*Anaerovorax*, ↑*Dorea*, ↓*Bifidobacterium*, ↓*Lactococcus*	
	Residue fraction from black raspberry	Rats	2.25% w/w in diet	6 weeks	↑*Anaerostipes*, ↑*Desulfovibrio*, ↑*Coprobacillus*, ↑*Victivallis*, ↑*Mucispirillum*, ↓*Streptococcus*, ↓*Turicibacter*, ↓*Acetivibrio*	
Blueberry	Wild blueberry drink (25 g of wild blueberry powder in 250 mL of water)	Human	Oral, 25 g/(day·person)	6 weeks	↑*Bifidobacterium* spp.	Vendrame et al. 2011
	Lowbush wild blueberry powder (*Vaccinium angustifolium*)	Rats	8% w/w in diet	6 weeks	↑*Bifidobacteriaceae*, ↑*Coriobacteriaceae*, ↓*Lactobacillus*, ↓*Enterococcus*	Lacombe et al. 2013
	Freeze-dried blueberry powder	Mice	5% w/w in diet	4 weeks	↑Tenericutes, ↓*Deferribacteres*	Wankhade et al. 2019
	Water-soluble blueberry extracts	Rats	Gavage, 4 g of extracts/(kg bw·day)	6 days	↑*Lactobacillus*, ↑*Bifidobacterium*	Molan et al. 2009
	Freeze-dried blueberry (*Vaccinium angustifolium*) pomace powder	Chicken	1% and 2% w/w in diet	64 days	↑Bacteroidetes, ↑*Lactobacillus*, ↑*Bifidobacterium*, ↓*Escherichia coli*, ↓*Clostridium_Clostridiaceae*, ↓*Helicobacter*, ↓*Enterococcus*	Islam et al. 2019

(*Continued*)

Table 1 (*Continued*)

Source	Whole foods or extracts	Model	Dose	Duration	Effects on gut microbiota	Reference
Cherry	Cherry concentrate juice	Human	Oral, 8 oz/day	5 days	High-*Bacteroides* individuals: ↓*Bacteroides*, ↓*Parabacteroides*, ↓*Alistipes*, ↓*Barnesiella*, ↓*Butyricimonas*, ↓*Odoribacter*, ↓*Porphyromonas*, ↓*Bifidobacterium*, ↑*Ruminococcus*, ↑*Lachnospiraceae*, ↑*Clostridium*, ↑*Clostridium* XI, ↑*Dialister*, ↑*Coprococcus*, ↑*Lactobacillus*, ↑*Streptococcus* Low-*Bacteroides* individuals: ↓*Lachnospiraceae*, ↓*Streptococcus*, ↓*Dialister*, ↓*Blautia*, ↓*Roseburia*, ↑*Bacteroides*, ↑*Prevotella*, ↑*Alistipes*, ↑*Clostridium* IV and XI, ↑*Lactobacillus*, ↑*Bifidobacterium*, ↑*Ruminococcus*	Mayta-Apaza et al. 2018
Citrus	Citrus pectin	Mice	15% w/w in diet	4 weeks	↑Bacteroidetes, ↓Firmicutes	Shtriker et al. 2018
	Orange juice	Human	Oral, 300 mL/(day·person)	2 months	↑*Lactobacillus* spp., ↑*Bifidobacterium* spp.	Lima et al. 2019
	Orange juice (*Citrus sinensis*)	Human	Oral, 500 mL/(day·person)	7 days	↑*Mogibacteriaceae*, ↑*Lachnospiraceae*, ↑*Ruminococcaceae*, ↑*Veillonellaceae*, ↑*Enterococcaceae*, ↑*Coriobacteriaceae*	Brasili et al. 2019
Cranberry	Freeze-dried whole cranberry powder	Human	Oral, 30 g/(day·person)	5 days	↓Firmicutes, ↑Bacteroidetes	Rodríguez-Morató et al. 2018
	Cranberry juice	Human	Oral, 200 mL/(day·person)	3 weeks	↓*Helicobacter pylori*	Gotteland et al. 2008
Kiwifruit	Freeze-dried green kiwifruit powder (without peel)	Pigs	25% w/w in diet	14 days	↑*Bacteroides*, ↓*Enterobacteria*, ↓*Escherichia coli*	Han et al. 2011
	Freeze-dried green kiwifruit fiber powder	Pigs	6.9% w/w in diet	14 days	↑*Bacteroides*	

(*Continued*)

Table 1 (*Continued*)

Source	Whole foods or extracts	Model	Dose	Duration	Effects on gut microbiota	Reference
	Freeze-dried green kiwifruit (*Actinidia deliciosa*) powder (without peel)	Rats	10% w/w in diet	4 weeks	↑*Lachnospiraceae*	Paturi et al. 2014
	Freeze-dried gold kiwifruit (*Actinidia chinensis*) powder (without peel)	Rats	10% w/w in diet	4 weeks	↑*Bacteroides–Prevotella–Porphyromonas* group, ↑*Enterococcus* spp.	
Hardy banana	Freeze-dried *Musa basjoo* powder (dissolved in 20 mL ddH_2O)	Mice	Gavage, 0.52, 1.04, 2.07 g/(kg bw·day)	7 weeks	↑*Bacteroides*, ↑*Roseburia*, ↓*Staphylococcus*, ↓*Helicobacter*	Wei et al. 2019
Pomegranate	Pomegranate extract	Human	Oral, 1,000 mg/(day·person)	4 weeks	↑*Actinobacteria*, ↑*Butyrivibrio*, ↑*Enterobacter*, ↑*Escherichia*, ↑*Lactobacillus*, ↑*Prevotella*, ↑*Serratia*, ↑*Veillonella*, ↓Firmicutes, ↓*Collinsella*	Li et al. 2015
	Pomegranate (*Punica granatum* L. Mollar de Elche cv.) juice	Human	Oral, 200 mL/(day·person)	4 weeks	No significant changes of microbiota	Mosele et al. 2015
Broccoli	Cooked broccoli	Human	Oral, 200 g/(day·person)	15 days	↑*Bacteroides*, ↑Bacteroidetes, ↓Firmicutes	Kaczmarek et al. 2019
	Freeze-dried broccoli powder	Rats	10% w/w in diet	4 days	↑*Akkermansia*, ↑*Oscillospira*, ↓*Clostridium*, ↓*Dorea*	Liu et al. 2017
Mushroom	Dried *Armillariella tabescens* powder	Pigs	0.1, 0.3, and 0.9% w/w in diet	30 days	↑*Lactobacillus* spp., ↑*Bifidobacterium* spp., ↓*Escherichia coli*	Chen et al. 2017
	Freeze-dried white button mushroom powder (*Agaricus bisporous*)	Mice	1% w/w in diet	4 weeks	↑Bacteroidetes, ↓*Clostridia*, ↓Firmicutes	Varshney et al. 2013
	Freeze-dried white button mushroom powder	Pigs	3 and 6 serving size in diet	6 weeks	↑*Lachnospiraceae*, ↑*Ruminococcaceae*, ↑*Porphyromonadaceae*, ↓*Bifidobacteriaceae*	Solano-Aguilar et al. 2018
	Freeze-dried *Pleurotus eryngii* powder	Mice	1 and 3% w/w in diet	6 weeks	↑Bacteroidetes, ↑*Deferribacteres*, ↓Firmicutes, ↓Verrucomicrobia	Hu et al. 2019
Soybean	Soybean flour	Rats	41.5% w/w in diet	14 days	↑*Prevotella*, ↑*Eubacterium*	Nakata et al. 2017

(Koutsos et al. 2017). Whole foods also modulate gut microbiota through inhibiting potentially harmful microorganisms. Cranberry intake (freeze-dried whole cranberry powder, 30 g/day for 5 days) in humans decreased the fecal abundance of bacteria associated with infection and antibiotic resistance, such as *Clostridia* and *Oribacterium* (Finegold et al. 2005, Rodríguez-Morató et al. 2018). Consumption of two apples per day for two weeks in human volunteers decreased the fecal abundance of lecithinase-positive clostridia, including *Clostridium perfringens*, a pathogen involved in food poisoning (Shinohara et al. 2010). Whole-food intake also showed inhibitory effects on potentially harmful bacteria in animal models. For example, lingonberries in the diet (20% w/w) caused a decrease in fecal abundance of *Lachnospiraceae*, *Ruminococcus*, and *Oscillospira* in mice. These microorganisms have been linked to obesity and type II diabetes (Heyman-Lindén et al. 2016). Oral administration of bitter melon (freeze-dried powder without seeds) to rats decreased the proportion of the potential endotoxin-producing opportunistic pathogens, such as *Escherichia*, in the fecal microbiota (Bai et al. 2016). Dietary treatment with green kiwifruit (freeze-fried powder) decreased the fecal abundance of *E. coli* (Han et al. 2011), and feeding white mushroom (freeze-dried powder) to mice decreased fecal abundance of *Clostridia* (Varshney et al. 2013).

It is well recognized that there are considerable interindividual variations in gut microbiota among humans. The difference in the gut microbiota composition may influence the response of individuals to the same dietary intervention. For example, intake of tart cherry juice induced distinct and inverse responses in gut microbiota among human participants who had different initial levels of *Bacteroides* prior to the dietary intervention (Mayta-Apaza et al. 2018). After tart cherry juice consumption, low-*Bacteroides* participants showed a decrease in *Lachnospiraceae*, *Ruminococcus*, and *Collinsella* and an increase in *Bacteroides* and *Bifidobacterium*, whereas high-*Bacteroides* participants showed opposite changes in fecal microbiota compared to that in low-*Bacteroides* participants, i.e., an increase in *Lachnospiraceae*, *Ruminococcus*, and *Collinsella* and a decrease in *Bacteroides* and *Bifidobacterium* (Mayta-Apaza et al. 2018). The mechanism underlying this interesting phenomenon warrants further investigation.

The alterations of gut microbiota induced by whole fruits and vegetables were mainly attributed to MACsand polyphenols found in these whole foods (Sonnenburg et al. 2016). The interactions between gut microbiota, MACs, and polyphenols are discussed below.

Interaction Between Microbiota-Accessible Carbohydrates and Gut Microbiota

MACs are generally indigestible by host-secreted intestinal enzymes and, therefore, reach the colon largely intact, where they serve as substrates for certain gut bacteria (Brinkworth et al. 2009). Fruits and vegetables are abundant in multiple types of MACs, such as oligosaccharides, pectin, cellulose, inulin, lignans, and resistant starches (Anderson et al. 2009). Gut microbiota is dominated by Firmicutes and Bacteroidetes, both of which contain bacteria that can utilize MACs (Flint et al. 2012). The availability of MACs promotes the growth of certain beneficial bacteria that can readily utilize these MACs as energy sources, whereas the bacterium-derived metabolites of MACs, such as SCFAs, may inhibit the growth of certain harmful bacteria. Consequently, the composition of the gut microbiota can be shaped by the availability of MACs in the colon. For example, low intake of MACs resulted in a remarkable decrease in taxa and diversity of gut bacteria relative to the results from high intake of MACs in humanized mice (Sonnenburg et al. 2016). High intake of MACs was associated with increased fecal abundance of Bacteroidetes, especially *Prevotella*, and depletion of Firmicutes in healthy children. Furthermore, children who consumed high levels of MACs had higher levels of fecal SCFAs, which were associated with lower abundance of fecal pathogens, such as *Escherichia* and *Shigella* (De Filippo et al. 2010).

Apples are rich in pectin, a soluble fiber (Koutsos et al. 2015). Consumption of two apples per day in human subjects increased fecal abundance of *Bifidobacterium* and *Lactobacillus*, elevated

production of SCFAs, and decreased abundance of *Enterobacteriaceae* and *Pseudomonas* (Shinohara et al. 2010). In vitro fermentation of apple pectin with human fecal bacteria also facilitated the growth of *Bifidobacterium* and *Lactobacillus*, suggesting that pectin in apples was, at least in part, responsible for changes in the gut microbial ecosystem observed in the apple-eating human subjects (Shinohara et al. 2010). Consumption of citrus pectin (15% w/w in the mouse diet) led to increased fecal abundance of Bacteroidetes and decreased abundance of Firmicutes (Shtriker et al. 2018). Cranberry is a rich source of dietary fiber. A randomized controlled crossover trial demonstrated that daily intake of 30 grams of freeze-dried whole cranberry powder (equivalent to 2.3 cups of fresh cranberry) in humans led to a lowered F:B ratio in the fecal microbiota (Rodríguez-Morató et al. 2018). Cranberry-derived soluble fiber xyloglucans supported the growth of *Bifidobacterium longum* (Özcan et al. 2017). Studies in rodents also supported the role of MACs in modulating gut microbiota. Six weeks of dietary intervention with fiber-rich white-button mushrooms increased the abundance of *Ruminococcaceae* and *Lachnospiraceae* families in mouse fecal microbiota (Solano-Aguilar et al. 2018). Bacteria from these two families are known to be able to utilize plant fibers to produce SCFAs (Eeckhaut et al. 2013, Walker et al. 2011). Additionally, oral administration of broccoli and potato fiber significantly increased the fecal abundance of *Bacteroides*, *Prevotella*, and *Porphyromonas* in rats, and, importantly, intake of broccoli fiber decreased the abundance of the potential pathogens, such as *C. perfringens*, *E. coli*, and *Enterococcus* spp. (Paturi et al. 2017). Fiber-rich diets may inhibit the growth of pathogens through the change in intestinal pH induced by the production of SCFAs (De Filippo et al. 2010, Duncan et al. 2009). Increased microbial diversity is often used as a marker of healthier gut microbiota (Gu et al. 2019). Hardy banana (*Musa basjoo*) is rich in resistant starch (Chockchaisawasdee & Poosaran 2013). Consumption of dried hardy banana powder by mice for three weeks led to higher α- and β-diversities as well as a decreased F:B ratio in the fecal microbiota of mice (Wei et al. 2019). These effects may be ascribed to the resistant starch in hardy banana. In support of this notion, a 17-week double-blind crossover human study demonstrated that daily intake of 33 grams of resistant starch (resistant starch types 4) for three weeks increased the fecal abundance of Bacteroidetes and lowered the fecal abundance of Firmicutes (Martínez et al. 2010).

One of the major functions of gut microbiota is to ferment MACs to produce SCFAs, primarily acetate, propionate, and butyrate. Members from Bacteroidetes and Firmicutes produce various enzymes capable of breaking down MACs to yield SCFAs, and SCFAs may positively influence gut microbiota and host gut health. The higher fecal levels of SCFAs in children consuming high amounts of MACs were found to be associated with lower abundance of pathogens (De Filippo et al. 2010). In line with this finding, a randomized, double-blind, placebo-controlled, parallel-group human trial showed that an enema with sodium butyrate during shigellosis led to improvement of rectal histopathology and early reduction of inflammation (Raqib et al. 2012). Furthermore, oral administration of sodium butyrate [200 mg/kg body weight (bw)] to mice increased the fecal abundance of potentially beneficial bacteria, such as *Christensenellaceae*, *Blautia*, and *Lactobacillus* (Zhou et al. 2017). Importantly, SCFAs also possess biological activities important to host health. The production of SCFAs is a means of recovering energy for the host body; for example, acetate can be absorbed by the liver and serve as a substrate for cholesterol synthesis (Gentile & Weir 2018). Dietary supplementation of SCFAs in obese rodents or humans was shown to result in promising beneficial effects. Administration of butyrate (5% w/w in diet) to mice inhibited high-fat-diet-induced body weight gain and insulin resistance and promoted energy expenditure (Gao et al. 2009). Oral intake of inulin-propionate ester, a means of delivery of propionate to the colon, for 24 weeks in humans prevented weight gain in overweight humans (Chambers et al. 2015).

Interactions Between Polyphenols and Gut Microbiota

Polyphenols are abundant in whole fruits and vegetables, and they play important roles in influencing the gut microbial community. Polyphenols (such as catechins) can be absorbed in the small intestine, and a significant portion is metabolized and excreted back to the intestinal lumen via efflux pumps in the intestinal epithelium and bile secretion from the liver. Conjugated and polymeric polyphenols (such as anthocyanins and proanthocyanidins) have low absorption in the upper gastrointestinal tract and can accumulate in the colon. In general, abundant amounts of dietary polyphenols reach the colon either intact or in the forms of their metabolites (Del Rio et al. 2013). Polyphenols and their metabolites interact with microbiota in the colon in a reciprocal manner, as bacteria can metabolize these compounds, and polyphenols and their metabolites can modulate microbiota composition and functions (Giménez-Bastida et al. 2012, Hanske et al. 2013). This reciprocal interaction has been linked to improved host health.

The impact of gut microbiota on polyphenols. The biotransformation of polyphenols by gut microbiota in the colon has been extensively studied in recent years. Various metabolites have been identified, and they may have different biological functions compared with their parent polyphenol compounds. This is the reason why biotransformation of polyphenols by gut microbiota may play an important role in mediating health effects of dietary polyphenols. For example, flavonoid glycosides can be transformed to aglycon, which is generally more bioavailable and more bioactive. Fission reactions mediated by gut bacteria lead to the breakdown of the ring structures of polyphenols and subsequent production of various phenolic acids that may convey bioactivities not offered by the intact polyphenols.

Although the chemical natures of polyphenols are diverse and complex, they can be broken down by gut microbiota to form much simpler structures, such as derivatives of phenylacetic, phenylpropionic, phenylbutyric, and valeric acids and urolithins (Hervert-Hernandez & Goñi 2011, Saura-Calixto et al. 2010, Tzounis et al. 2008). Feeding freeze-dried powders of cranberry, blueberry, or black raspberry to rats resulted in urinary excretion of approximately 20 different phenolic acids, with hippuric, 4-hydroxyphenylacetic, 4-hydroxy-3-methoxyphenylacetic, and 4-hydroxyphenylpropionic acids being the most common (Khanal et al. 2013). The production of these phenolic acids was ascribed to the microbial breakdown of polyphenols in those berries, and the relative urinary abundance of different phenolic acids was dependent on berry types. The production of microbial metabolites of berry polyphenols was also investigated in humans, and the results showed similarities as well as differences between rodents and humans in response to dietary consumption of whole berries. Oral intake of wild blueberry powder (22 grams per day) in humans for 30 days significantly increased plasma levels of benzoic, 2,5-dihydroxybenzoic, vanillic, hippuric, and 3-hydroxyhippuric acids, whereas no significant change was observed in the urinary levels of these metabolites (Feliciano et al. 2016, Mosele et al. 2015). In contrast, the urinary level of hippuric acid increased approximately sixfold, whereas those of 2,5-dihydroxybenzoic and vanillic acids did not change after oral intake of blueberry powder in rats (Khanal et al. 2013). In another human study, consumption of cranberry powder (30 grams per day) for five days increased urinary levels of 3,4-dihydroxyphenylacetic and 4-hydroxy-3-methoxyphenylacetic acids (Rodríguez-Morató et al. 2018), whereas cranberry-fed rats showed increased urinary levels of 4-hydroxy-3-methoxyphenylacetic acid but not of 3,4-dihydroxyphenylacetic acid (Khanal et al. 2013). The difference in microbial metabolites of berry polyphenols between rodents and humans may be attributed to differences in gut microbiota composition and host metabolism of polyphenols. Along with phenolic acids, many other types of microbiota-derived polyphenol metabolites

have been identified, and there are still others that remain to be identified. Their contribution to human health is an important topic that warrants further investigation.

To better understand the mechanism of microbiota-mediated biotransformation of polyphenols, it is important to identify the strains of bacteria and their genes/enzymes responsible for the production of specific metabolites of polyphenols. For example, colonic bacteria can produce multiple enzymes, such as β-glucuronidase, responsible for various deconjugation reactions of polyphenols such as β-glucuronidase (Aura 2008, Ilett et al. 1990), β-glucosidase (Clavel et al. 2006), esterases (Andreasen et al. 2001), hydrogenases (Walle et al. 2004), dehydroxylase (Clavel et al. 2005b, 2006), and demethylase (Clavel et al. 2005b, 2006; Keppler & Humpf 2005). *Eubacterium ramulus* and *Clostridium saccbarogumia* were able to convert cyanidin 3-glucoside, a common anthocyanin from berry fruits, to 3,4-dihydroxybenzoic acid and 2,4,6-trihydroxybenzaldehyde (Hanske et al. 2013). *Streptococcus thermophilus* and *Lactobacillus plantarum* broke down mulberry anthocyanins to form chlorogenic acid, caffeic acid, and ferulic acid (Cheng et al. 2016). *Bifidobacterium lactis* and *Lactobacillus gasseri* produced cinnamoyl esterase that converted chlorogenic acid to hydroxycinnamate and ferulic acid (Couteau et al. 2001). Although information on specific gut microorganisms and the genes responsible for the production of bioactive polyphenol metabolites is accumulating, the overall understanding of this subject remains preliminary, which significantly limits our ability to elucidate the complex interplay between dietary components and gut microbiota.

Modulation of gut microbiota by polyphenols from whole fruits and vegetables. As a class of major bioactive components of fruits and vegetables, polyphenols may modulate gut microbiota through stimulation of beneficial bacteria and inhibition of pathogens. The effects of polyphenol-rich extracts of fruits and vegetables on gut microbiota have been studied in humans and animals. The administration of 1% (w/w in diet) of grape seed extract in pigs for six days altered gut microbiota composition, i.e., increased abundance of potentially beneficial bacteria, such as *Lachnospiraceae*, *Ruminococcaceae*, and *Lactobacillus* (Choy et al. 2014). *Lachnospiraceae* and *Ruminococcaceae* are two families of bacteria in the order Clostridiales that may produce SCFAs by fermenting dietary fiber, thereby potentially promoting intestinal health (H. Zeng et al. 2017). The early-life supplementation of a grape pomace extract (200 mg/kg bw by daily gavage for 12 days) in mice caused inhibition of *norank_f_Lachnospiraceae*, *unclassified_f_Lachnospiraceae*, and *Mucispirillum* as well as a promotion of *Akkermansia* and *Lactobacillus* in the fecal microbiota (Lu et al. 2019). The increased abundance of *Mucispirillum* was associated with elevated inflammatory biomarkers and colitis (M. Zeng et al. 2017). Some members of *Lachnospiraceae* were linked to diet-induced obesity and positively correlated with diabetes (Kameyama & Itoh 2014, Rom et al. 2017). Oral gavage of a bilberry anthocyanin extract (20 mg/kg bw per day for 10 weeks) to rats increased the fecal abundance of some bacteria potentially beneficial to the host, such as *Lactobacillus*, *Bacteroides*, *Clostridiaceae*-1, the Bacteroidales-*S24*–7 group, and the *Lachnospiraceae_NK4A136* group, and at the same time reduced the abundance of potentially harmful bacteria, such as Verrucomicrobia and Euryarchaeota (Li et al. 2019). Furthermore, thirty-nine postmenopausal women consumed 100 mg of dietary isoflavones daily for two months to characterize changes in microbial communities of the intestinal tract. The supplementation elevated the abundance of dominant microorganisms of the *Clostridium coccoides–Eubacterium rectale* cluster, *Lactobacillus–Enterococcus* group, and *Bifidobacterium* genus, and these organisms were considered beneficial to human health (Clavel et al. 2005a). The lower F:B ratio implies a non-obese and healthier status. The consumption of a grape seed proanthocyanidin extract (500 mg/kg bw, daily gavage for 8 days) increased the cecal abundance of Bacteroidetes and Proteobacteria and decreased the F:B ratio in rats (Casanova-Martí et al. 2018). In a human study, twenty healthy participants were supplemented with 1,000 mg

of a pomegranate extract daily for four weeks, which delivered pomegranate polyphenols in an amount equivalent to approximately eight ounces of pomegranate juice. It was observed that the pomegranate extract significantly decreased the fecal abundance of Firmicutes (Li et al. 2015).

The metabolites of polyphenols produced by microorganisms in the large intestine may also impact gut microbiota. *Yersinia enterocolitica* is an enteropathogen in humans and mammals and causes gastrointestinal infections after the consumption of contaminated foods (Rahman et al. 2011). Urolithins are gut microbiota–derived metabolites of ellagic acid. Urolithin-A and urolithin-B inhibited quorum sensing–mediated processes such as biofilm formation and swimming motility in *Y. enterocolitica*, which suggested that urolithins may exert anti-pathogenic effects against *Y. enterocolitica* in the gut (Giménez-Bastida et al. 2012). It is important to point out that the aforementioned anti-pathogenic effects of urolithins were observed at the concentrations of urolithins achievable in the intestinal tract through a regular diet.

Whole Foods versus Isolated Major Components of Whole Foods in Modulating Gut Microbiota

The impact of whole foods on gut microbiota is the result of combined actions of all bioactive components of whole foods such as MACs and polyphenols. Because of the potential interactions among these components, the biological effects produced by whole foods may be different from the sum of actions of individual components of the whole foods, for example, synergistic or antagonistic effects may be produced when different components interact with each other, which may lead to unpredictable biological outcomes. Many studies investigated the biological functions of extracts of fruits and vegetables. However, doses of extracts used in these studies were often much higher than those achievable through regular consumption of whole foods, which produces results not likely to be relevant to whole-food consumption. Furthermore, most of these studies ignore the potential synergistic or antagonistic interactions between the isolated extracts and other components existing in the same whole foods, which may lead to the underestimation or overestimation of their effects. In addition, the combination of different components from different whole foods may also potentially confer different bioactivities if ingested together. For example, dietary fiber and polyphenols from different fruits and vegetables when consumed together can interact with each other, so that fiber can entrap polyphenols and protect them from absorption and metabolism in the small intestine. When fiber and polyphenols reach the colon, together they may induce a stronger prebiotic response from gut microbiota, and microbiota-mediated polyphenol metabolism and fiber fermentation together may produce enhanced health outcomes compared with those produced by fiber or polyphenols alone. In a rat study, dietary treatments that combined with an anthocyanin-rich extract from blackcurrant and fibers from apple or broccoli were found to produce enhanced anti-obesity effects compared to anthocyanin or fiber alone (Paturi et al. 2018).

Despite the biological significance of food component interaction, the mode of interaction among different components of whole foods in modulating gut microbiota has not been adequately studied and therefore remains largely unknown. A recent study compared the effects of dietary intake of whole black raspberry (freeze-dried powder) and two of its major bioactive fractions, namely the anthocyanin fraction and residue fraction (mainly fibers), on the composition of gut microbiota in rats (Pan et al. 2017). The rats were fed whole black raspberry (5% w/w in diet), anthocyanin fraction (0.2% w/w in diet), or residue fraction (2.25% w/w in diet) for six weeks. The doses of anthocyanins and residue fractions were equal to their wt% contribution to the whole black raspberry powder. Interestingly, different fractions of black raspberry led to distinct effects on gut microbiota. Both the whole black raspberry and residue fraction elevated the fecal abundance of *Akkermansia* and *Desulfovibrio*, which were both associated with the anti-inflammatory

effect (Liu et al. 2016, Song et al. 2016), whereas the anthocyanin fraction did not. This finding suggested that the residue fraction was at least partially responsible for the increased abundance of *Akkermansia* and *Desulfovibrio*. The fecal abundance of *Anaerostipes*, a butyrate producer (Rivière et al. 2016), was increased by whole black raspberry, whereas the anthocyanin fraction or residue fraction showed no effect. These results suggested that black raspberry components other than the anthocyanin or residue fractions might be responsible for the change in *Anaerostipes*, and/or combined effects of the anthocyanin and residue fractions were needed to modulate the abundance of *Anaerostipes*. It is noteworthy that the same types of fruits and vegetables may significantly vary in their compositions depending on, e.g., cultivation locations, climates, and harvest time, which may lead to inconsistent results among studies using the same types of whole fruits and vegetables. For example, dietary intake of different batches of lingonberries resulted in remarkably different effects on gut microbiota in mice (Heyman-Lindén et al. 2016).

WHOLE FOODS AND GUT MICROBIOTA–ASSOCIATED DISEASES

Obesity

Gut microbiota are a critical factor in the development of obesity. The lack of gut microbiota in germ-free mice resulted in resistance to the Western diet–induced obesity (Bäckhed et al. 2007), indicating a pivotal role of gut microbiota in obesity. The obesity-associated microbiota were found to have a higher capacity for energy harvest, and higher energy intake than expenditure may lead to obesity (Turnbaugh et al. 2006). As the dominant phyla of gut microbiota, both Firmicutes and Bacteroidetes are capable of degrading MACs to produce SCFAs. A higher F:B ratio was observed in obese mice and humans (Turnbaugh et al. 2006). Furthermore, production of SCFAs in the colon might induce obesity by enhancing lipid synthesis (Bäckhed et al. 2004). Dietary intake of whole fruits and vegetables was reported to impact obesity through the modulation of gut microbiota. **Table 2** lists the alterations of gut microbiota in obese rodents and humans induced by dietary intervention with various whole fruits and vegetables.

The relative abundance of Firmicutes and Bacteroidetes in gut microbiota is considered an important marker in the development of obesity. An increase in Firmicutes and a decrease in Bacteroidetes were reported in obese mice and humans with high BMIs (Ley et al. 2006, Turnbaugh et al. 2006). In obese mice, Bacteroidetes abundance was 50% lower than that in lean mice, and the microbiota in obese mice was associated with a more effective capacity to release calories than that in lean mice (Ley et al. 2006). A human study showed an inverse correlation between Bacteroidetes abundance and body weight (Ley et al. 2006). Members of Firmicutes (such as *Ruminococcaceae*, *Lachnospiraceae*, *Clostridium*, and *Lactococcus)* and Bacteroidetes (such as *Prevotella*, *Bacteroides*, and *S24–7*) have been studied in terms of their potential contributions to the development of obesity. Consumption of whole foods produced anti-obesity effects and resulted in a decreased abundance of Firmicutes and its members, such as *R. gnavus* (via navy bean consumption) (Monk et al. 2019) and *Clostridium* (via tomato and pomegranate juice consumption) (Li et al. 2018). Intake of whole foods increased abundance of Bacteroidetes and its members in obese mice. For example, consumption of lingonberry or strawberry increased abundance of *Bacteroides* (Marungruang et al. 2018, Matziouridou et al. 2016, Petersen et al. 2019), and consumption of cherry, lingonberry, or navy bean increased abundance of *Prevotella* and *S24–7* (Garcia-Mazcorro et al. 2018, Heyman-Lindén et al. 2016, Monk et al. 2019).

Although the lowered F:B ratio has been used to indicate an anti-obesity profile of gut microbiota, it is worth mentioning that emerging evidence has supported the use of other microbiota-related markers to characterize obesity status. Contrary to the expected low F:B ratio in lean individuals, a human study showed a lowered F:B ratio in overweight and obese individuals

Table 2 The effects of whole fruits and vegetables on gut microbiota in obesity models

Source	Animal model	Dose	Duration	Biomarkers	Effects on gut microbiota	Reference
Avocado	Overweight/obese human	Oral, 1 avocado/(day·person)	12 weeks	Decrease in IL-1β, C-reactive protein, and hepatic growth factor	↑*Dialister*, ↑*Sutterella*, ↑*Bilophila*, ↑*Holdemanella*, ↑*Herbaspirillum*, ↑*Acetivibrio*, ↓*Methanosphaera*	Henning et al. 2019
Bitter melon (*Momordica charantia* L.)	High-fat-diet-induced obesity in rats	Gavage, 300 mg/(kg bw·day)	8 weeks	Decrease in fasting glucose, HOMA-IR, TNF-α, IL-6, MCP-1, and LPS concentration; increase in IL-10	↓*Proteobacteria*, ↓*Desulfovibrionaceae*, ↓*Enterobacteriaceae*, ↓*Escherichia*, ↑*Odoribacteraceae*, ↑*Allobaculum*, ↑*Butyricimonas*, ↑*Faecalibacterium*, ↑*Odoribacter*	Bai et al. 2016
Bitter melon	High-fat-diet-induced obesity in mice	1.5% w/w in diet	16 weeks	Decrease in macrophage infiltration, sphingokinase1 mRNA, IL-1β, and NLRP 3 inflammasome components	↑Bacteroidetes, ↑*Clostridiaceae*, ↑*Porphyromonadaceae*, ↑*Ruminococcus*, ↑*Lactobacillus*, ↓Firmicutes, ↓*Actinobacteria*, ↓*Eubacteriaceae*, ↓*Oscillibacter*, ↓*Blautia*,	Nerurkar et al. 2019
Bitter melon (*M. charantia* L.)	High-fat-diet-induced obesity in rats	Gavage, 400 mg/(kg bw·day)	8 weeks	Decrease in LBP and HOMA-IR	↑Verrucomicrobia, ↑*Blautia*, ↑*Anaerotruncus*, ↑*Lactococcus*, ↑*Allobaculum*, ↑*Oceanobacillus*, ↓*Prevotella*, ↓*Anaeroplasma*	Bai et al. 2018

(*Continued*)

Table 2 (*Continued*)

Source	Animal model	Dose	Duration	Biomarkers	Effects on gut microbiota	Reference
Blueberry	High-fat-diet-fed rats	10% w/w in diet	8 weeks	Increase in ilea villus, *Mucin 2*; decrease in TNF-α, IL-1β	↑*Actinobacillus*, ↑*Aggregatibacter*, ↑*Fusobacteriaceae*, ↑Lactobacillales, ↑*Porphyromonadaceae*	Lee et al. 2018
Broccoli	High-fat-diet-induced obesity in rats	7.5% w/w in diet	17 weeks	Decrease in body weight gain	↑*Bifidobacterium* spp., ↑*Lactobacillus* spp.	Paturi et al. 2010
Grape	High-fat-diet-induced obesity in mice	3% and 5% w/w in diet	11 weeks	Decrease in body fat and TG; increase in ZO-1	↓*Desulfobacter* spp., ↓*Bilophila wadsworthia*, ↑*Akkermansia muciniphila*	Baldwin et al. 2016
Lingonberry (*Vaccinium vitis-idaea* L.)	High-fat-diet-induced obesity in mice	20% w/w in diet	11 weeks	Decease in plasma levels of glucose and cholesterol, serum amyloid, and LBP	↑*Akkermansia*, ↑*Faecalibacterium*, ↑*S24–7*, ↑*Parabacteriodes*, ↑*Odoribacter*, ↓Firmicutes/ Bacteroidetes ratio, ↓*Ruminococcus*, ↓*Oscillospira*, ↓*Bacteroides*, ↓*Lachnospiraceae*	Heyman-Lindén et al. 2016
Mango (*Mangifera indica* L.)	Obese individuals	Oral, 400 g/ (day ·person)	6 weeks	Trend toward decreased endotoxin	Trend toward decreased *Bacteroides thetaiotaomicron*	Barnes et al. 2019
Mango	High-fat-diet-induced obesity in mice	1% and 10% w/w in diet	12 weeks	Increase in IL-10 and plasma insulin; no effect on glucose tolerance and body weight	↑*Bifidobacterium*, ↑*Akkermansia*, ↑*Aldercrutzia*	Ojo et al. 2016

(*Continued*)

Table 2 (*Continued*)

Source	Animal model	Dose	Duration	Biomarkers	Effects on gut microbiota	Reference
Mushroom	High-fat-diet-induced obesity in mice	0.5% and 3% w/w in diet	4 weeks	Decrease in adipocyte size and perinephric adipose tissue	Trend toward increased *Allobaculum*, *Bifidobacterium*, *Ruminococcus*, *Lactobacillus*, *Lactococcus*, and *Streptococcus* and decreased *Bacteroides*, *Prevotella*, *Mucispirillum*, *Dorea*, *Roseburia*, *Escherichia*, and *Akkermansia*	Shimizu et al. 2018
Navy bean	High-fat-diet-induced obesity in mice	15.7% w/w in diet	12 weeks	Increase in ZO-1, occluding, and mucins; decrease in HOMA-IR, adipocyte size, NFkBp65, and STAT3	↑*Akkermansia muciniphila*, ↑*Prevotella*, ↑*S24–7*, ↓*Ruminococcus gnavus*	Monk et al. 2019
Spinach	High-fat-diet-induced NAFLD in rats	2.5% and 5% w/w in diet	5 weeks	Decrease in fasting glucose, and LDL cholesterol	↑*Lactobacillus*	Elvira-Torales et al. 2019
Tomato	$BCO1^{-/-}/BCO2^{-/-}$ mice	4.19% w/w in diet	24 weeks	Decrease in pathological severity of steatosis, hepatic TG, TNF-α, IL-1β, and IL-6	↓*Clostridium* sp. ID4, ↓*Clostridium*	Li et al. 2018

Abbreviations: HOMA-IR, homeostatic model assessment for insulin resistance; IL, interleukin; LBP, LPS-binding protein; LDL, low-density lipoprotein; MCP, monocyte chemoattractant protein; NAFLD, non-alcoholic fatty liver disease; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP, Nod-like receptor protein; TG, triglyceride; TNF, tumor necrosis factor; ZO-1, zonula occludens-1.

compared with that in lean individuals (Schwiertz et al. 2010). Fibers can be fermented by both Firmicutes and Bacteroidetes, such as *Lactobacillus* and *Ruminococcus* from Firmicutes and *Prevotella* and *S24–7* from Bacteroidetes (Flint et al. 2015, Louis et al. 2007); thus, both Firmicutes and Bacteroidetes may thrive in the presence of fiber-rich whole foods. Oral administration of mushroom powders inhibited obesity in mice, but it did not lower the F:B ratio (Shimizu et al. 2018). This might be due to the increase of the abundance of Firmicutes genera *Lactobacillus*, *Lactococcus*, and *Ruminococcus* in the presence of mushroom fibers (Shimizu et al. 2018). Avocado- and bitter melon–fed obese rats significantly lost body weight, but they did not show a lowered F:B ratio compared with the lean rats (Bai et al. 2016, Henning et al. 2019). These results supported the use of markers other than the F:B ratio to indicate an anti-obesity microbiota profile. For example, the *Prevotella* to *Bacteroides* ratio was used to predict weight loss success in humans (Hjorth et al. 2019). Interestingly, the number of fecal SCFAs has been considered as a microbiota-related marker of obesity in humans because colonic production of SCFAs correlated well with the BMIs and the levels of SCFAs are in accordance with the alteration of gut bacteria (Duncan et al. 2007, Schwiertz et al. 2010).

As shown in **Table 2**, *Akkermansia*, a Gram-negative bacterium belonging to Verrucomicrobia, has attracted increasing attention in terms of its role in obesity. Calorie restriction followed by a weight-stabilizing diet improved the metabolism status of overweight and obese volunteers, which was accompanied by increased fecal abundance of *Akkermansia muciniphila* (Dao et al. 2016). The fecal abundance of *A. muciniphila* is inversely correlated with body weight in rodents and humans, and the oral administration of *A. muciniphila* alleviated high-fat-diet-induced metabolic disorder, which includes increased fat mass, inflammation in adipose tissue, metabolomic endotoxemia, and insulin resistance (Garcia-Mazcorro et al. 2018, Heyman-Lindén et al. 2016, Monk et al. 2019). Obesity was associated with reduced mucus thickness in the mouse intestinal tract (Everard et al. 2013), suggesting increased gut permeability. Oral administration of *A. muciniphila* in obese mice restored the thickness of mucus and enhanced the gut barrier function; furthermore, it improved glucose homeostasis and adipose tissue metabolism (Everard et al. 2013). Interestingly, the protein Amuc_1100, isolated from the outer membrane of *A. muciniphila*, was capable of recapitulating the beneficial effects of *A. muciniphila* through interaction with Toll-like receptor 2 to improve gut barrier function (Plovier et al. 2017).

Consumption of whole fruits and vegetables was found to increase the fecal abundance of *A. muciniphila*. For example, oral intake by obese mice of cherry (Garcia-Mazcorro et al. 2018), lingonberry (Heyman-Lindén et al. 2016, Marungruang et al. 2018, Matziouridou et al. 2016), grape (Baldwin et al. 2016), mango (Ojo et al. 2016), or navy bean (Monk et al. 2019) decreased body weight and increased the fecal abundance of *A. muciniphila*, indicating that the anti-obesity actions of these whole fruits and vegetables might be closely related to their effects in promoting the growth of *A. muciniphila*. The high levels of fibers in these whole foods might contribute to the blooming of *A. muciniphila* in the colon (Desai et al. 2016). Furthermore, dietary polyphenols from fruits may also promote the growth of *A. muciniphila* in the colon, which was associated with their anti-obesity and anti-colonic inflammation potential (Roopchand et al. 2015).

Colonic Inflammation

In the host, gut microbiota homeostasis is required to maintain health. When the balance of the bacterial community in the colon becomes disrupted, it may trigger abnormal immune responses and induce colonic inflammation (Cerf-Bensussan & Gaboriau-Routhiau 2010). For example, certain species of bacteria are considered to stimulate colonic inflammation, and the increase in these bacteria, e.g., pathogenic *E. coli*, is associated with colonic inflammation (Prorok-Hamon et al. 2014). In contrast, several strains of *Bifidobacterium* and *Lactobacillus* can produce

anti-inflammatory effects by modulating the inflammation-related cell-signaling pathways (Rodes et al. 2013), and the ample presence of these bacteria in the gut may protect the host against colonic inflammation. Colonic inflammation was associated with a reduction in Firmicutes (Sokol et al. 2008), Bacteroides (Sokol et al. 2008), *Bifidobacterium adolescentis* (Joossens et al. 2011), *Faecalibacterium prausnitzii* (Sokol et al. 2008), or *Lactobacillus* and *Eubacterium* (Sha et al. 2013), and an increase in *Enterobacteriaceae* and *R. gnavus* (Joossens et al. 2011, J. Li et al. 2014). Studies have supported the notion that whole fruits and vegetables may inhibit colonic inflammation via modulating related gut bacteria. Administration of whole cranberry powder or strawberry powder in the diet of dextran sulfate sodium (DSS)-treated mice for six weeks increased fecal abundance of *Lactobacillus* and *Bifidobacterium*, which was associated with suppression of colonic inflammation (Cai et al. 2019, Han et al. 2019, Peran et al. 2006). In a genetically induced colitis mouse model, dietary consumption of blueberry or broccoli powder (10% w/w in diet) remarkably reduced the fecal abundance of *C. perfringens* and *E. coli* (Paturi et al. 2012), and the abundance of these bacteria was positively associated with colonic inflammation (Eichner et al. 2017, Prorok-Hamon et al. 2014). The anti-inflammatory potential of whole foods in the colon may stem from (*a*) bioactive components in whole foods, (*b*) altered gut microbiota induced by whole foods, and/or (*c*) microbiota-derived metabolites of whole-food components. For example, anthocyanin-rich fractions from red raspberry showed anti-inflammatory effects against lipopolysaccharide (LPS)-induced inflammation in macrophages, which was evidenced by the suppression of nitric oxide (NO) synthesis as well as the downregulation of inducible NO synthase (iNOS), cyclooxygenase-2, IL (interleukin)-1β, and IL-6 (L. Li et al. 2014). Probiotic *Bifidobacterium* suppressed inflammation both in vitro and in vivo (Damaskos & Kolios 2008, Okada et al. 2009). Fermentation of MACs from whole foods by gut bacteria produces SCFAs, especially butyrate, that showed anti-inflammatory effects through inhibition of the NFκB (nuclear factor kappa–light-chain-enhancer of activated B cells) pathway and regulation of T-cell functions (Furusawa et al. 2013, Segain et al. 2000). It is noteworthy that these three modes of action often coexist in the colon and are likely to interact with each other, producing modified health outcomes compared with those produced by each mode of action alone. Recently, an increasing number of studies demonstrated the anti-colonic inflammation effects of whole fruits and vegetables, such as cranberry, strawberry, mushroom, and anthocyanin-containing potatoes (Cai et al. 2019, Han et al. 2019, Hu et al. 2019, Sido et al. 2017, Wu et al. 2018). However, the detailed mechanistic understanding of how whole-food components and gut microbiota interact to produce inhibitory effects against colonic inflammation is lacking and therefore warrants further investigation.

Probiotics, such as *Bifidobacterium* and *Saccharomyces*, have been shown to offer protective effects against colonic inflammation (Damaskos & Kolios 2008). Furthermore, probiotics supplemented with food components might produce synergistic effects to confer benefits to the host. For example, a synbiotic supplementation containing whole-plant sugarcane fiber and *Bacillus coagulans* induced a stronger suppression of colonic inflammation than either whole-plant sugarcane or *B. coagulans* alone (Shinde et al. 2019). *Akkermansia*, an emerging probiotic, has demonstrated anti-inflammatory effects in the colon by stimulating mucin production and improving gut barrier (Everard et al. 2013, Shin et al. 2014, Thursby & Juge 2017). Patients with colonic inflammation showed a lower fecal abundance of *Akkermansia* (Rajilić-Stojanović et al. 2013). Oral administration of *Akkermansia* to DSS-treated mice ameliorated colonic inflammation, which was evidenced by the lower colon histological score and reduced colonic levels of proinflammatory cytokines (Zhai et al. 2019).

Although *Akkermansia* showed consistent protective effects against obesity and diabetes, the role of *Akkermansia* in colonic inflammation remains controversial. For example, a higher abundance of *Akkermansia* has been found in patients with IBD and colitic mice compared with healthy

DSS: dextran sulfate sodium

LPS: lipopolysaccharide

NO: nitric oxide

iNOS: inducible nitric oxide synthase

IL: interleukin

NFκB: nuclear factor kappa–light-chain-enhancer of activated B cells

counterparts (Danilova et al. 2019, Håkansson et al. 2015, Zella et al. 2010). A possible explanation is that the decreased thickness of mucus layer in the inflamed colon led to the outgrowth of *Akkermansia* (Ottman et al. 2017); consequently, the growth of *Akkermansia* in the lumen is elevated because of its access to ample substrates in the stool (Swidsinski et al. 2008). In line with these findings, colitic mice had a higher fecal abundance of *Akkermansia* than noncolitic mice, and consumption of whole strawberry or cranberry inhibited the colonic inflammation and decreased the fecal abundance of *Akkermansia* (Cai et al. 2019, Han et al. 2019). It is also possible that the protective effects of whole berries against colonic inflammation maintained the integrity of the colonic tissue, which in turn prevented migration of *Akkermansia* from mucus to the lumen (Garcia-Mazcorro et al. 2018). A recent study showed that oral administration of *A. muciniphila* induced colitis in germ-free IL10$^{-/-}$ mice by degrading mucus and producing LPS in the colon (Seregin et al. 2017). This finding was the opposite of that of another report, where oral gavage of *A. muciniphila* inhibited colitis in mice (Zhai et al. 2019). Different cellular components of *Akkermansia* were found to exert distinct functions in colon health. For example, the outer membrane of *Akkermansia* was reported to induce inflammation by upregulating proinflammatory cytokines (IL-1β and IL-6) in bone-marrow-derived macrophages (Seregin et al. 2017), whereas Amuc_1100 protein isolated from the outer membrane of *Akkermansia* improved the gut barrier in high-fat-fed mice (Plovier et al. 2017). These findings highlight the complexity of gut microbiota and its role in host health.

CONCLUSIONS

Intake of whole foods, such as fruits and vegetables, profoundly modulates the composition and functions of gut microbiota. These alterations of gut microbiota may (*a*) produce better health in disease-free populations to lower the risks of various diseases and (*b*) alleviate the disease severity in patients with microbiota-associated diseases such as obesity and IBD. MACs and polyphenols are the two major types of components responsible for the modulating effects of fruits and vegetables on gut microbiota. They have reciprocal interactions with gut microbiota in which MACs and polyphenols alter the structure of microbiota and microbiota transform MACs and polyphenols to bioactive metabolites such as SCFAs and phenolic acids, respectively. These microbiota-derived metabolites promote host health by targeting both host tissues and gut microbiota. Furthermore, the coexistence of whole-food components, their metabolites, and the microbiota in the large intestine provides opportunities for them to interact and produce certain biological functions that are otherwise impossible. The relationship among whole foods, gut microbiota, and the host is complex, which makes it challenging to study. Nevertheless, a highly interdisciplinary and dynamic approach giving special consideration to the physiological relevance of the experimental conditions is needed to elucidate the role of whole foods in modulating gut microbiota and associated diseases.

DISCLOSURE STATEMENT

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